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## FURTHER OBSERVATIONS ON AURICULAR FLUTTER

By W. T. RITCHIE

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the Research Laboratory of the Royal College of Physicians of Edinburgh

With Plates 1 and 2

SINCE the publication in 1905 of my first communication (16) on a case presenting rapid, rhythmic, auricular beats at a rate of 274.7 per minute, and more especially since 1911, when Jolly and I (7) recorded the electro-cardiographic evidence that the rhythmic and greatly accelerated action of the auricles in this case was closely similar to the fluttering of the auricles under faradic stimulation, as described by MacWilliam (13), auricular flutter has been recognized as occurring not infrequently in the human heart. In a more recent paper (18) I recorded three further cases of this disorder, and a fifth case is described in the present communication. Lea (9) has recorded a case with an auricular rate of 260 per minute. Lewis (10) reports eight cases, with auricular rates of 300-324, 280, 265-324, 270, 300, 330, 228, and 260 respectively. Hume (6) records one case in whom the auriculo-ventricular ratio was usually 260-130; Hay (4) refers to four cases, one of whom had an auricular rate of 260; Goteling Vinnis (22) reports a case with an auricular rate of 350; and in Fahrenkamp's (2) case the auricular rate was 240 per minute. If to these twenty-one cases we add the earlier cases recorded by Gibson (3) (one), Morison (14) (one), Hertz and Goodhart (5) (one), Rihl (15) (three), and Mackenzie (12) (No. 37 of his series), and the two cases (Turnbull (21), Lewis and Schleiter (11)) which Lewis (10) subsequently regarded as flutter, we have a total of thirty cases recorded.

In the following communication further observations are recorded on two cases of auricular flutter that have been reported previously (7, 18), and a new case is described.

### *I. Auricular Flutter observed for seven and a half years.*

In Case I of my series (7, 18), a man who is now 64 years of age and has mitral incompetence and complete heart-block, auricular flutter continued, except on two occasions, uninterruptedly for seven and a half years. The recorded auricular rates from 1905 until August, 1910, have been given elsewhere (7). Those subsequently recorded are given in Table I. From a comparison of electro-cardiograms it is evident that the auricular beats have undergone, of late,

[Q. J. M., Oct., 1913.]

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a notable change in rate and in the form and amplitude of their electro-cardiographic deflexions. In all the records from June, 1905, until July, 1911, the accelerated auricular rate was usually 250 to 276 per minute, rising to 300 on one occasion, and only once falling as low as 234.6 per minute. During the period from August, 1911, until December, 1912, the recorded auricular rates did not rise above 244.9 nor fall below 229.5 per minute. A notable decrease of rate, however, has occurred since March, 1913, the usual rate since then being 190 to 194, and the maximum being 201 per minute.

While the rate has fallen, there have also been changes in the form, and a lessening in the amplitude, of the auricular deflexions. In all the electro-cardiographic records from August, 1909, until the end of 1912, namely while the auricular rate was relatively quick, the form of the auricular deflexions, as recorded by each derivation, was constant. By derivation *I* there was a simple rise and fall with a value of 60 to 70 microvolts (Plate I, Fig. 1); by derivations *II* and *III* there was a diphasic curve having a total value of about 200 microvolts (Plate I, Figs. 3, 5). In the more recent records of the slower auricular rates, however, the auricular deflexions by derivation *I* are so small as to be hardly recognizable (Plate I, Fig. 2), while by derivations *II* and *III* the deflexions are no longer uniformly diphasic and have a value not exceeding 100 microvolts (Plate I, Figs. 4, 6). These changes in the auricular activity have ensued without the administration of any drug, and have been accompanied by a relative enfeeblement of the ventricles, as manifested by the onset of cyanosis, cough, and venous congestion in the lower lobe of the left lung.

When the auricular rate was relatively frequent (250 to 300 per minute), no further acceleration was induced by means of atropin, nor was the rate retarded by means of vagus compression. When the rate was relatively infrequent (187 to 201 per minute), however, atropin accelerated it slightly and strophanthin retarded it markedly (Table I). The initiation of the less frequent auricular rhythm, therefore, was under vagus control, whereas that of the more frequent rhythm was not. Taking into consideration this fact together with the changes in rate and form of the auricular deflexions, it is probable that the two rhythms were not initiated at the same site. If the chronotropic influence of the vagus upon the auricles is exerted solely through the sino-auricular node, the site of initiation of the slower rhythm was presumably nearer the node than that of the faster rhythm. Moreover, in view of the striking differences between the fast auricular rhythm (flutter) and the slow, it seems advisable to regard the latter as a form of auricular tachysystole different from true flutter.

TABLE I.

*Analysis of Records from a Case of Auricular Flutter and Complete Heart-block.*

Date.	Rate per minute.		Remarks.
	Auricles.	Ventricles.	
1910, September 16	250.0	55.3	Group-beating of the ventricles.
October 10	253.8	60.5	" " "
November 16	250.0	55.3	" " "
December 27	250.0	50.5	Neither " right nor left vagus compression retards auricles or ventricles.
1911, February 8	250.0	62.5	Group-beating of the ventricles.
April 24		36.5	Ventricles rhythmic.
April 27	252.6	41.5	Ventricles rhythmic. Before inhalation of amyl nitrite.
	256.4	41.4	After inhaling amyl nitrite for four minutes.
May 11		45	Maximum systolic pressure, 165; diastolic pressure, 125 mm. Hg.
July 10	277.7	32.4	Respiratory rate the same as the ventricular.
July 17	267.0	33.5	Ventricles rhythmic.
August 18	242.8	37.9	" "
October 26	232.7	33.9	" "
November 1	232.4	33.6	" "
November 15	229.5	32.0	Ventricles rhythmic. Had been taking 30 minims of tincture of squill daily since October 19.
December 8	244.9	37.4	Ventricles rhythmic.
1912, January 4	244.9	52.4	Ventricles arrhythmic.
January 8	244.9	39.3	Ventricular beats often coupled.
August 22	244.8	55.7	Plate I, Fig. 1.
September 25	244.4	38.2	Plate I, Figs. 3, 5.
October 22	242.5	38.0	Ventricles arrhythmic.
December 16	235.7	32.7	Ventricles rhythmic except for an occasional premature beat.
1913, March 10	190.5	44.8	Group-beating of the ventricles.
April 11	194.8	47	Numerous premature ventricular beats (Plate I, Figs. 2, 4, 6).
April 24	194.8	35.7	Ventricles rhythmic.
May 2	201.0	34.9	" "
May 9	192.6	42.4	Group-beating of the ventricles.
May 13	187.8	31.7	Ventricles rhythmic.
May 19	192.8	33.3	2.32 p.m.
	189.0	40.3	2.35 p.m.
	189.4	42.4	2.40 p.m.
			2.42 p.m. 0.03 grain atropin sulphate, subcutaneously.
	192.8	37.9	2.52 p.m.
	193.5	40.6	3.2 p.m.
	195.9	41.4	3.8 p.m.
	197.8	42.0	3.14 p.m.
May 21	190.5	31.3	11.0 a.m.
			11.5 a.m. 0.001 gramme strophanthin (Boehringer) intravenously.
	92.1	29.0	1.35 p.m.
	119.6	41.0	1.40 p.m.



## II. *The Morbid Anatomy of the Heart in a Case of Auricular Flutter.*

The chief clinical features of this case (No. III of my series) have been recorded fully elsewhere (18). It will therefore suffice to note that the patient was a cabman, aged 37, who had suffered from acute rheumatism three times, and who presented the physical signs of mitral stenosis and incompetence associated with cyanosis, dyspnoea, dropsy of the feet, and occasional palpitation. Ten days before his death the physiological sequence of the auricular contractions, at a rate of 92 to 98 per minute, was found to be replaced by an auricular flutter with a rate of 320, while the ventricular beats occurred rhythmically at a rate of 160 per minute. An intravenous injection of strophanthin was given, and on the following day the auricles were in fibrillation. Twenty-four hours later they had regained their physiological rhythm, and so far as could be determined they retained it until the fatal issue ensued.

At the post-mortem examination recent fibrinous pericarditis was found over the surface of the right auricle. All the chambers of the heart were dilated. The segments of the tricuspid valve were thick and shrunken; the pulmonary orifice measured 8 cm. in circumference; its valve was healthy. The mitral orifice was constricted, measuring only 3 cm. in circumference; the mitral cusps were thick, shrunken, and partially calcified. The chordae tendineae were also thickened and shortened, and the papillary muscles were somewhat fibrous. The aortic cusps were likewise thick and shrunken, but they were not calcareous. In the pars membranacea septi no abnormality was visible to the naked eye. The walls of the coronary arteries and their branches contained atheromatous patches, in some of which calcareous deposits were detected on microscopic examination. Portions of the wall of the right auricle above the marginal cusp of the tricuspid valve, of the left auricle, and of the lateral wall of the left ventricle presented a slight degree of fibrosis. In the wall of the right ventricle the fibrous patches were more numerous and larger.

*The sino-auricular node.* After the heart had been fixed in Pick's fluid a large block containing the right and posterior portions of the lower part of the superior caval wall and the adjacent part of the right auricular wall was cut out, hardened in alcohol, and split in the longitudinal axis of the superior vena cava into five portions, each of which was subsequently embedded in paraffin and cut in serial section. As a rule every tenth section was mounted and stained with iron-haematoxylin and with picro-fuchsin or with eosin; but some sections were stained with Unna's polychrome methylene-blue and differentiated with acid-alcohol.

The portions of tissue examined contained the whole of the node. It was situated on the posterior and right posterior aspects of the auricular wall, somewhat below the cavo-auricular junction, and lay immediately subjacent to the epicardial connective tissue except at its lower and posterior pole, where it became buried in the auricular musculature. Still further back, behind and below the level at which the well-defined node ended, there were many muscle fibres, of



the same size and structural characters as those of the node, scattered throughout the loose connective tissue on the endocardial aspect of the auricular wall. At all parts of the cavo-auricular junction there were numerous large nerves and groups of ganglion cells in the sub-epicardial connective tissue. Some of these were in the immediate vicinity of the node.

Both on the distal and the proximal side of the cavo-auricular junction the epicardium was considerably infiltrated with lymphocytes, together with a few plasma cells and an occasional polymorpho-nuclear leucocyte. This cellular infiltration, which was most pronounced at the angle between the superior vena cava and the auricular appendix, extended inwards through the caval and the auricular walls more or less diffusely. The infiltration of the auricular musculature was nowhere very intense, but it certainly involved the node and the nerves at the cavo-auricular junction. The auricular muscle also presented a moderate degree of diffuse fibrosis.

*The auriculo-ventricular bundle system.* The portion of septal wall that contained the auriculo-ventricular node, the bundle, and the upper parts of its main branches was embedded in celloidin and cut into 400 serial sections parallel to the upper margins of the aortic cusps. One hundred and twenty of these sections were examined after having been stained with iron-haematoxylin and with picro-fuchsin or with eosin.

Throughout the auricular muscle above and below the node there was a slight degree of diffuse interfascicular fibrosis, with slight lymphocytic infiltration of the loose connective and adipose tissues. The cellular infiltration became more intense at an area immediately behind the thickened, fibrous, anterior cusp of the mitral valve. At this area the bundles of muscle fibres and the dense fibrous tissue separating them one from another were markedly infiltrated with lymphocytes. The adjacent endocardium on the left side of the auricular septum was thickened, vascularized, and moderately infiltrated with lymphocytes and plasma cells.

The auriculo-ventricular node, measuring 1.7 mm. transversely and about 2.7 mm. antero-posteriorly, lay on the right lateral aspect of the auricular septum, subjacent to the sub-endocardial connective tissue. It presented no abnormality save a minimal lymphocytic infiltration, which was decidedly less intense than that occurring elsewhere in the auricular septum. The artery to the node, passing into it from above and behind, was healthy.

The bundle took its origin from the anterior end of the node, and measured 1.3 mm. in diameter. It passed forwards, downwards, and to the left through the dense fibrous septum until, eventually, it lay close to the left lateral wall of the septum, where it became somewhat flattened and was enclosed, except on its right side, by a sheath of loose connective tissue. Just below the deepest part of the pars membranacea septi the right branch was given off. It passed downwards and towards the right side. Its transverse section was of ovoid form and measured 0.9 by 0.5 mm. The uppermost part of this branch was surrounded by a loose connective-tissue sheath, but at lower levels there was

only a thin sheath of compact fibrous tissue. The branch lessened rapidly in diameter until, when lying in the sub-endocardial tissue on the right side of the heart, its transverse diameter was only 0.3 mm. The left branch—the more direct continuation of the main stem—spread out fanwise on the left side of the septum, was 0.4 mm. thick, and was enclosed in a well-marked sheath of loose connective tissue.

The greater portion of the main stem and the dense fibrous tissue it was traversing presented no evidence of any inflammatory or degenerative changes. But the basal portion of the septal cusp of the tricuspid valve was the seat of a pronounced subacute inflammation, being thickened, vascularized, and densely infiltrated with lymphocytes and plasma cells. This inflammatory process spread so far through the septal wall as to involve slightly the terminal portion of the auriculo-ventricular bundle and the initial portions of both branches. Lower down, the branches were almost entirely uninvolved. The ventricular muscle, however, presented a slight degree of fibrosis and lymphocytic infiltration.

It is evident, therefore, that the various pathological changes in the substance of the heart were the results of (1) old-standing coronary disease, (2) endocarditis spreading from the mitral valve into the auricular septum, (3) endocarditis extending inwards from the tricuspid valve so as to involve slightly the auriculo-ventricular bundle and its branches, and (4) acute pericarditis spreading inwards at the cavo-auricular junction and thus implicating the sino-auricular node and the abundant nerve elements in that region.

### III. *A Case presenting Transitions between Auricular Flutter, Fibrillation, and an intermediate Form of Auricular Activity.*

R. S., a miner, aged 38 years, was admitted on February 8, 1913, to the Wards in the Royal Infirmary of Edinburgh under the care of Dr. William Russell, to whom I gratefully express my indebtedness for permission to record the case.

The patient was a married man with four healthy children. His only antecedent illness was an attack of acute rheumatism, lasting for four months, twelve years previously. At times he had been immoderate in the use of alcohol. For three weeks before his admission to hospital he had experienced shortness of breath, pain at the lower part of the sternal region, and a choking sensation in the same region, 'as if a lump were there which he could not swallow.' The act of deglutition, however, was not attended by any difficulty or pain, and his appetite was good. He had not suffered from palpitation or faintness, nor had there been any dropsy.

On admission to hospital he was found to be a rather poorly nourished man of 5 feet 7 inches, weighing 143 lb. His complexion was pale, and although the ears and nose were of a red tint there was no cyanosis. The cardiac impulse was widespread, forcible, and usually irregular, the point of maximum impulse being in the sixth left intercostal space 4 inches from the mid-sternal line. The only endocardial murmur was a rough diastolic murmur, of mitral origin, which became audible during the longer diastolic pauses. The walls of the radial and brachial arteries presented a moderate degree of diffuse



thickening, and the systolic arterial pressure was equal to 140 mm. Hg. The lungs, abdomen, urine, and nervous systems presented no abnormal features.

During the first four days the patient was in hospital, his ventricular action, although sometimes rhythmic, was usually irregular, and was constantly accelerated (see Table II). When the ventricles were beating rhythmically the auricles were in flutter, there being a ratio of As:Vs::2:1. When the ventricles were irregular the auricles were either in fibrillation or in a form of activity intermediate between flutter and fibrillation. During his stay in hospital the patient took fourteen Nativelle's granules, each containing  $\frac{1}{240}$  grain of digitalin. In the course of a few days he obtained entire relief from all his symptoms, and on the eighteenth day of his residence, when his pulse was still irregular and accelerated, and when he was still taking one granule daily, he expressed himself as feeling perfectly well and insisted on returning home. Thus no opportunity was afforded of observing the nature of the auricular action after the digitalin was discontinued.

Attention may be directed to some features of this case that are of particular interest.

1. *The auricles.* Three forms of auricular action were observed—flutter, fibrillation, and an intermediate form.

(a) *Flutter* was recorded by derivations II and III. By both derivations the auricular deflexions were rhythmic, of large amplitude (200 microvolts), of constant form except when distorted by ventricular deflexions, and usually occurred at a rate of 339–343 per minute. On one occasion, immediately after the auricles had passed from fibrillation into flutter, the auricular rate was as high as 377.2 per minute.

When the ratio of As:Vs was 2:1 the auricular deflexions were distorted by those of ventricular origin, and thus the true nature of the heart's action was somewhat obscured. The auricular flutter was revealed clearly, however, when the ventricles were retarded by means of pressure on the right vagus in the neck. This is illustrated in Plate II, Fig. 1. The record starts with fifteen rhythmic ventricular beats at a rate of 169.7 per minute. The corresponding beats of the brachial pulse are hyperdicrotic but not alternating. The auricular rate, meanwhile, is exactly twice that of the ventricles, namely 339.4 per minute. The summits of successive *P* deflexions fall 0.14 second after the commencement of *R* and synchronously with the summit of *T* respectively. Pressure upon the right vagus slows the ventricles markedly. The longer of the two prolonged ventricular diastoles lasts for 1.75 seconds. While the ventricles are retarded the auricular deflexions continue rhythmically at a rate of 342.8 per minute, which is approximately the same rate as that before pressure was applied to the vagus.

The initial auricular deflexion is upwards; there are two summits, of which the second is the higher. The curve then descends below, and subsequently regains, the level at which *Q* starts. In some instances the line of descent is arrested momentarily at that level, so that the auricular deflexions are diphasic. The total value of the deflexion is 200 microvolts. In this record the As:Vs ratio is 2:1, 2:1, 2:1, 2:1, 10:1, 12:1, 4:1.

When the auricles were in flutter no record of the effects of pressure on the left vagus was obtained.

(b) *Fibrillation*. The auricular deflexions, as a rule, occurred at a rate of about 415 to 467 per minute. They were either small and markedly irregular in form and rhythm (fine fibrillation) or larger (50–150 microvolts) and less irregular in form and rhythm (coarse fibrillation).

(c) *The form intermediate between flutter and fibrillation* was characterized by auricular deflexions at a rate of about 367 per minute, of fairly constant but not diphasic form, of considerable amplitude (about 150 microvolts) and almost wholly rhythmic. Between this form and coarse fibrillation on the one hand and flutter on the other there were no hard and fast lines of distinction. This form of auricular activity is probably identical with the combination of co-ordinate contraction and fibrillation in the dog's auricle which Rothberger and Winterberg (20) term 'unreines Schlagen'.

Transitions from fibrillation to flutter and vice versa occurred repeatedly, and were recorded in several instances. The transition was not sudden, but on the contrary gradual. In Plate II, Fig. 3, for example, there is at first a fine fibrillation; gradually it becomes coarser, and the auricular deflexions become not merely larger but less irregular and eventually rhythmic, until at the end of the record they have the same form and rhythm as in the initial portion of Plate II, Fig. 1, where the auricles are obviously in flutter. Another example of transition from fibrillation to flutter is shown in Plate II, Fig. 2. Transitional forms between auricular flutter and fibrillation have also been recorded in the human heart by Fahrenkamp (2), in the dog's heart by Canby Robinson (19), and in the cat's heart by Korteweg (8). These observations will be discussed in a later part of this paper.

2. *The ventricles*. When the auricles were in flutter the ventricles beat rhythmically at a rate of 169.7–171.6 per minute, there being a constant ratio of As:Vs::2:1. On one occasion immediately after the cessation of auricular fibrillation, a ventricular rate of 188.6, with an auricular rate of 377.2 per minute, was recorded (Plate II, Fig. 2). When the auricles were in fibrillation the ventricular contractions were arrhythmic and less frequent, their rate varying from 76 to 107.1 per minute. When the auricular action was intermediate between flutter and fibrillation the ventricular rhythm was, at first sight, wholly irregular, but occasionally the length of some of the inter-ventricular periods was an exact multiple of the average P-P interval, suggesting that a regular auricular rhythm predominated occasionally. Thus in Plate II, Fig. 3, where the average P-P interval is about 0.14 second, the inter-ventricular periods are—

0.59, 0.42, 0.69, 0.89, 0.80, 0.70, 0.42, 0.42, 0.45, 1.12, 0.98, 0.45, 0.38, 0.35 sec.  
= 0.14 × 3                      5    3    3                      8    7

In another record, of which a portion is reproduced in Plate I, Fig. 7, the rate



of the auricular deflexions was about 367.1 per minute, and the interventricular periods were—

$$\underbrace{0.63, 0.64, 0.73, 0.94}_{2.00}, \underbrace{0.60, 0.63, 0.87}_{2.10}, \underbrace{0.45, 0.91, 0.63}_{1.99} \text{ second.}$$

The grouping of the beats is almost exactly constant, which suggests that there is a regular dominant rhythm of the auricles.

When the auricles were fluttering, the arterial pulse was small and hyper-dicrotic, but never alternating. On one occasion, when fibrillation was passing into flutter, some of the ventricular beats were not represented in the sphygmogram (Plate II, Fig. 3). Once, when the auricles were in fibrillation, and once again when their action was of the intermediate form (Plate I, Fig. 7), ventricular extra-systoles of the second variety (Einthoven (1)) were recorded. These intensified the irregularity of the ventricular rhythm.

3. *The effects of vagus stimulation.* (a) *On the fluttering auricles.* In a former paper (17) I have stated the evidence that led me to conclude that any factor, such as vagus stimulation, which depresses conductivity in the auricles may cause blockings in their walls, whereby inco-ordinate, fibrillar contraction of irritable muscle fibres may ensue. Experimental observations demonstrate that an auricular flutter may be transformed into fibrillation by means of vagus stimulation. Thus Korteweg (8) has observed that if the vagi be stimulated while the cat's auricles are being faradized the auricular action assumes a form intermediate between 'tachysystole' and fibrillation. In the dog's heart similar intermediate forms of auricular action have been studied by Rothberger and Winterberg (20), and more fully by Canby Robinson (19). The latter found that 'auricular tachycardia' set up by faradization became replaced by fibrillation when the right, but not the left, vagus was stimulated, and that soon after the right vagus stimulation ceased there ensued a peculiar combination of definite contractions involving at least the main mass of auricular musculature together with either fibrillary movements or weak peristaltic waves—the 'unreines Schlagen' described by Rothberger and Winterberg (20).

The effects of vagus stimulation upon the human heart may be obtained either by means of compression upon the vagus in the neck, or by means of drugs such as digitalis and strophanthus. In the case now recorded, as well as in all other cases of auricular flutter recorded hitherto, vagus compression has failed to influence the auricles. On the fluttering auricles, therefore, vagus compression exerts no apparent inhibitory effects. On the ventricles the effects are well marked.

The last column in Table II shows that in the present instance an auricular activity varying from flutter to fibrillation became replaced by a more permanent fibrillation under the influence of digitalin. This effect is probably due to vagus stimulation, for it is the same as that induced by stimulation of the nerve experimentally. In a number of other recorded instances auricular flutter is



known to have been transformed into fibrillation by means of digitalis or strophanthus, and it is not improbable that many cases of persistent auricular fibrillation have passed through an unrecognized phase of auricular flutter.

(b) *On the fibrillating auricles.* In one record of left vagus compression, the coarse auricular fibrillation became finer during the period of prolonged ventricular standstill. Canby Robinson (19) has obtained similar effects by stimulating the right vagus in the dog.

(c) *On the ventricles.* In the present case compression of the right vagus, although failing to influence the fluttering auricles, caused a notable retardation of the ventricles. This has been described on p. 8, and is shown in Plate II, Fig. 1.

When the auricles were in fibrillation, compression of the right vagus, on two separate occasions, was wholly ineffective in retarding the ventricles. On the only occasion when left vagus compression, lasting for 2.5 seconds, was recorded the ventricular retardation was very striking, for the interventricular periods changed from 0.63, 0.59, 0.66, 0.42 to 0.59, 0.66, 2.52, 0.84, 0.70 second. The effects obtainable by vagus compression in man, however, are not sufficiently constant to permit of any definite deduction from these tests regarding differences in the mode of action of the two vagi.

#### *Summary.*

I. In one case auricular flutter, at a rate usually of 250-276 per minute, persisted almost uninterruptedly for seven and a half years. The auricles meanwhile were not under vagus control. The flutter has now been replaced by an auricular tachysystole at a rate of 187-201 per minute, the form of the auricular deflexions has changed, and the auricles are under vagus control.

II. The pathological changes are described in a heart that had presented auricular flutter ten days before death. There were slight, diffuse inflammatory processes in the myocardium. Both nodes, the bundle and its branches, were slightly affected.

III. The clinical and electro-cardiographic features are described in a new case presenting transitions between auricular flutter, fibrillation, and an intermediate form of auricular activity.

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#### DESCRIPTION OF FIGURES.

PLATE 1, FIGS. 1, 3, 5. Electro-cardiograms from Case I, by derivations *I* (Aug. 22, 1912), *II* (Sept. 25, 1912), and *III* (Sept. 25, 1912) respectively, showing auricular flutter and complete heart-block. In these figures the auricular rates are 244.8, 244.4, and 244.4 per minute, and the total value of the auricular deflexions about 70, 200, and 200 microvolts respectively. In Figs. 3 and 5 the auricular deflexions are diphasic.

FIGS. 2, 4, 6. Electro-cardiograms recorded on April 11, 1913, from Case I, by derivations *I*, *II*, and *III* respectively. In Fig. 2 the auricular deflexions are inconspicuous. In Figs. 4 and 6 the auricular rates are 194.8 and 197.7 per minute respectively, and the value of the auricular deflexions is about 100 microvolts.

FIG. 7. Brachial pulsations and electro-cardiogram recorded by derivation *III* on February 11, 1913, from the case described in section III of this paper. The auricular activity is of the form intermediate between flutter and fibrillation, being represented by fairly rhythmic deflexions at a rate of about 367.1 per minute. One ventricular extra-systole (*Ex*) of the second variety is recorded.

In Figs. 1-6, 1.5 cm. equals 1 millivolt; in Fig. 7, 1 cm. equals 1 millivolt. In all the figures the time record is 28.57 per second.

PLATE 2, FIGS. 1, 2, 3, from the case described in section III of this paper. In Figs. 1 and 2, 1.5 cm. equals 1 millivolt; in Fig. 3, 1 cm. equals 1 millivolt. The time record is 28.57 per second.

FIG. 1. Brachial pulsations and electro-cardiogram by derivation *III* (February 12, 1913). The signal shows the time during which pressure was applied to the right vagus. The auricular flutter persists throughout at a rate of 339.4-342.8 per minute, whereas the ventricles are retarded by vagus compression.

FIG. 2. Electro-cardiogram by derivation *III* (February 10, 1913). During the first long ventricular diastole the auricles are in fibrillation. This passes into flutter at a rate of 377.2 per minute, with a ratio of *As* : *Vs* :: 2 : 1.

FIG. 3. Brachial pulsations and electro-cardiogram by derivation *III* (February 14, 1913). Auricular fibrillation becoming coarser and eventually passing into flutter (see pp. 9 and 10).



FIG. 1

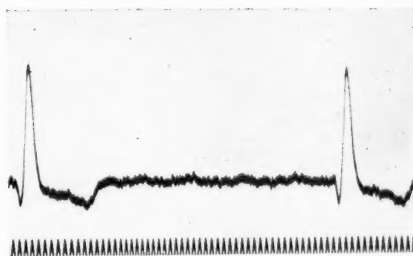


FIG. 2

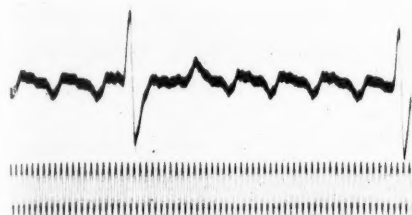


FIG. 3



FIG. 4

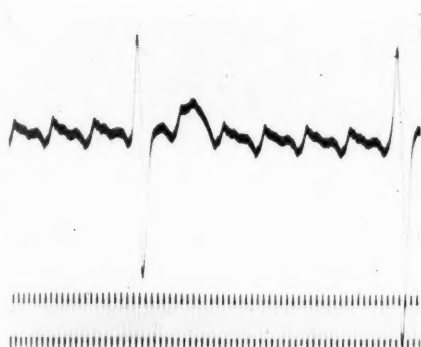


FIG. 5

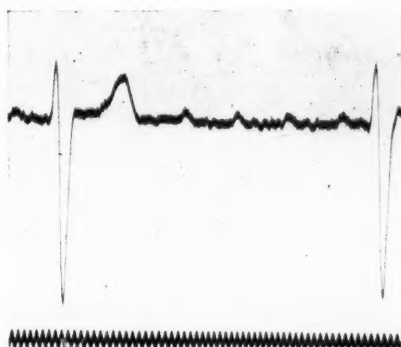


FIG. 6

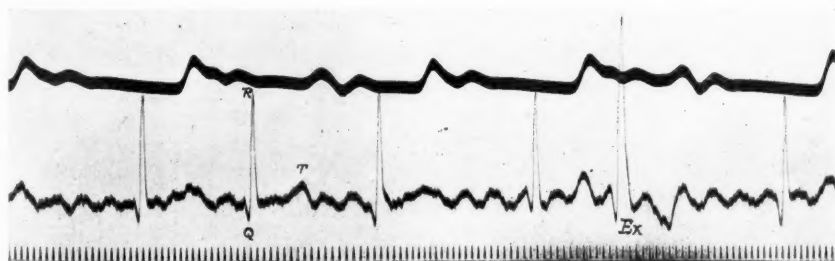


FIG. 7



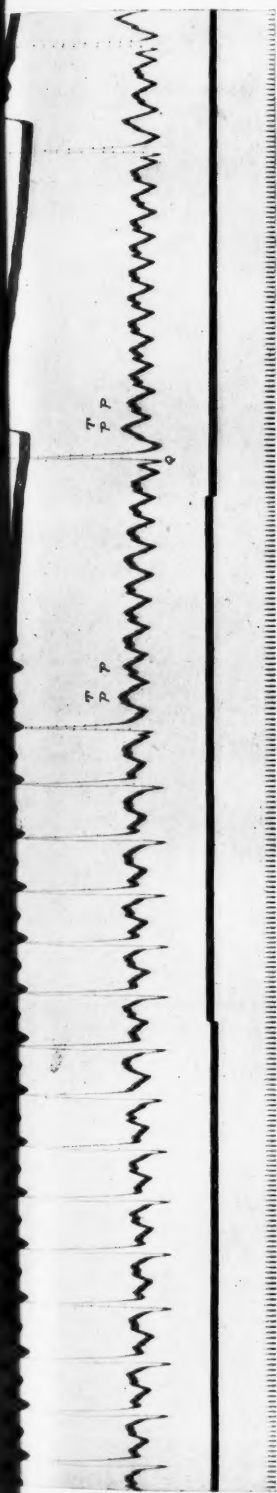


FIG. 1

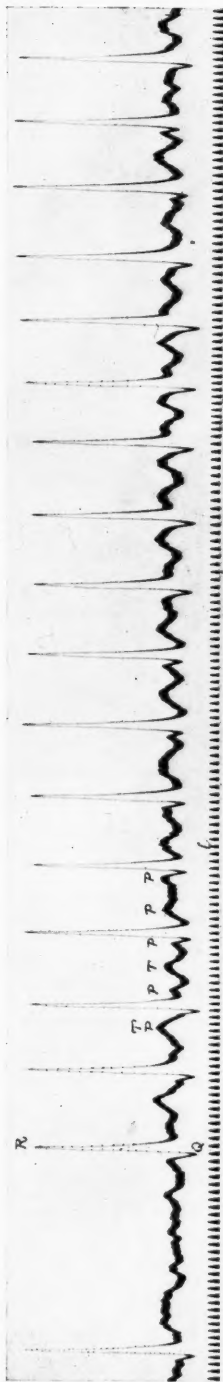


FIG. 2

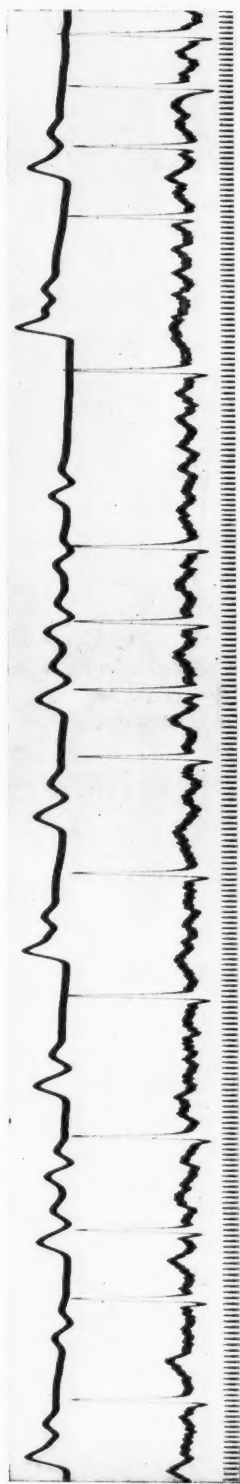


FIG. 3

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## ON THE VARIATIONS IN THE EXCRETION OF ENDOGENOUS URIC ACID PRODUCED BY CHANGES IN DIET

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THE amount of uric acid excreted in the urine by man, when a purin-free diet is taken, was stated by Burian and Schur (2), and by Siven (17), working independently, to be almost a constant quantity, varying, however, with the individual. Burian and Schur considered that the sum of the uric acid and purin bases was rather more constant than the uric acid alone. They also stated that the output of total purins might be altered by abnormal conditions. The views of Burian and Schur, and Siven, have been supported by the work of other observers, and, with the exception of Maurel (14), Leathes (13), and Folin (6), they all agree that the output of uric acid is not dependent on the amount of nitrogen excreted.

The abnormal conditions in which the uric acid metabolism is altered have been further investigated. It has been shown by Schreiber and Waldvogel (16), Hirschstein (8), Cathcart (3), and Feldman (5), that in starvation there is a sudden and well-marked fall in the uric acid output. After a few days, however, it gradually rises and again reaches the normal value (Cathcart).

Folin has observed that when a purin-free diet containing very little protein and about 2,000 calories of fat and carbohydrate is eaten, the uric acid output is much decreased. Thus, in three cases the uric acid was decreased by over 45 per cent., in two by over 36 per cent., in one by 20 per cent., and in one, which was complicated by acute mania, it was little altered. In two other cases when a different diet was eaten the fall in the uric acid output was insignificant, although the total nitrogen output was much reduced.

In the course of some experiments on 'The Influence of High Temperature on Protein Metabolism with reference to Fever' we determined the nitrogen distribution in the urine produced by different diets (7). In two experiments a diet was taken which corresponded to that given by Folin, except that the calorie value was increased to 4,600 by means of lactose and extra starch and cream. The total nitrogen output in the two experiments was reduced to 3.39 gm. and 2.78 gm. nitrogen, and the uric acid fell to 0.10 gm. nitrogen

<sup>1</sup> Working under the tenure of a Beit Memorial Fellowship.

and 0.088 grm. nitrogen respectively. The results, therefore, confirm Folin's observations.

In a third experiment a diet of 1,800 calories was eaten which contained protein (12 grm. nitrogen) and fat, but no carbohydrates. The uric acid in this experiment fell to an even lower figure than was obtained in the other experiments.

The result seemed so remarkable that we have each of us repeated the experiment, and we now give the figures for these three experiments in the tables on pp. 15-17:

#### *The Total Nitrogen Output.*

The influence of a diet containing only protein and fat and of insufficient calorie value is well shown in these experiments. In each case the nitrogen output rose rapidly and the greatest amount was excreted on the third day. The nitrogen output then fell for the next five days. The nitrogen intake was approximately the same in the three experiments, i. e. 12.27 grm., 11.41 grm., and 11.44 grm., and the calorie values were 1,910, 1,390, and 2,350. The figures for the three experiments were strikingly similar and the output for the seventh day was 14.87 grm., 14.25 grm., and 14.38 grm. respectively. The figures for Experiment II show that the nitrogen output had fallen to a steady level by the time the experiment was stopped, and it was possible that the same was true in the other experiments. The amount of nitrogen lost in the three experiments was also about the same. In eight days, in Experiments I and II, 36.98 grm. of nitrogen were lost, while in Experiment III 33.98 grm. of nitrogen were lost in seven days. These results are in agreement with those obtained by Landergren (13), and show that the action of fat in sparing protein metabolism is very different from that of carbohydrate.

#### *The Uric Acid Output.*

In Experiments I and II the diet taken was not quite purin-free, as 17 grm. of cocoa were added. Cocoa contains theobromine, and the methyl anthines are scarcely, if at all, converted into uric acid by man (Brusch and Schittenhelm (1)), so that the effect of the cocoa may be neglected. The general effect of the diet on the uric acid excretion was similar in each case, although there were some individual variations. In Experiment I the uric acid was not estimated on the first day, and on the second day it had fallen to 0.09 grm. nitrogen. On the fourth day it rose to 0.136 grm., but on the last four days of the experiment it was below 0.09 grm. nitrogen and reached 0.069 on the eighth day. The average excretion from the second to fourth day was 0.112 grm., and that for the last four days was 0.079 grm. nitrogen.

In Experiment II the uric acid was 0.18 grm. nitrogen on the first day, and after falling to 0.12 grm. on the third day, it rose to 0.14 grm. on the fourth day. On the fifth day it fell to 0.096 grm., and was below 0.10 grm. on the next three

TABLE I  
Experiment I (Experiment IV of last Paper). Date, March 23-April 4, 1912.  
Subject G. G.

Day of Expt.	Body Weight in kilos.	Vol. of Urine in c.c.	N. Intake. Grm.	Total N. Urine. Grm.	Total N. Faeces. Grm.	N. Balance. Grm.	Uric acid. Grm. of N.	Ammonia. Grm. of N.	Aceto-acetic Acid. Grm.	$\beta$ -oxybutyric Grm.	% of Total Acetone Bodies.	Total Acetone Bodies reckoned as $\beta$ -oxybutyric Acid. Grm.
0	—	1420	—	11.04	—	—	—	—	—	—	—	—
1	62.4	2098	12.27	13.25	1.37	-2.35	—	—	—	—	—	—
2	61.3	960	12.27	16.19	1.37	-5.29	0.282	0.34	0.49	0.199	22.6%	0.699
3	—	1213	12.27	17.84	1.37	-6.94	0.315	0.39	0.52	0.311	36.8%	0.844
4	60.6	1250	12.27	16.58	1.37	-5.68	0.408	0.28	0.537	0.328	37.4%	0.877
5	—	1521	12.27	15.77	1.37	-4.87	0.252	0.39	0.778	0.593	43.7%	1.389
6	60.4	1796	12.27	15.26	1.37	-4.36	0.255	0.43	0.684	0.329	32.7%	1.029
7	—	1774	12.27	14.87	1.37	-3.97	0.231	0.39	0.673	0.454	39.8%	1.142
8	59.2	1663	12.27	14.31	1.37	-3.41	0.207	0.43	0.736	0.466	39.5%	1.208
					Total	-36.87						

The following diet was eaten during this experiment:—

Plasmon	80 gm.	9.18 gm. N.	286 cal.
Cocoa	17 gm.	0.7 gm. N.	88 cal.
Cream	342 gm.	1.39 gm. N.	1500 cal.
Egg	1	1.0 gm. N.	85 cal.
Salt	12 gm.	—	—

12.27 gm. nitrogen.  
1909 calories.

The figures for the last 3 days of the Experiment are not given here, as a temperature of 104° F. was induced on the ninth day for the purposes of the research.

TABLE II  
*Experiment II. Date, Aug. 23-Sept. 4, 1912.*  
*(Subject G. G.)*

Day of Expt.	Vol. of Urine in c.c.	Calorie Value.	N. Intake. Grm.	Total N. in Urine. Grm.	Total N. in Faeces.	N. Balance. Grm.	Uric Acid. Grm. of N.	Aceto-acetic Acid. Grm.	$\beta$ -oxybutyric Grm.	$\beta$ -oxybutyric % of Total Acetone Bodies.	Total Acetone Bodies reckoned as $\beta$ -oxybutyric Acid. Grm.
0	1458	—	—	12.2	—	—	—	—	—	—	—
1	1215	1840	11.89	13.65	1.12	-2.88	0.546	0.144	—	—	—
2	1620	1840	11.89	16.0	1.12	-5.23	0.398	0.623	—	—	—
3	2020	1840	11.89	16.68	1.12	-5.91	0.364	1.03	—	—	—
4	1310	1390	11.41	15.48	1.12	-5.19	0.421	0.140	0.557	36%	1.56
5	1770	1390	11.41	15.42	1.12	-5.13	0.287	0.096	1.98	59.6%	3.31
6	1650	1390	11.41	14.61	1.12	-4.32	0.213	0.071	2.28	59.2%	3.85
7	1180	1390	11.41	14.25	1.12	-3.96	0.195	0.065	1.78	54%	3.8
8	1500	1390	11.41	14.65	1.12	-4.36	0.302	0.101	1.25	52.2%	2.39
						-36.98					
9	1485	3040	11.89	11.08	1.12	-0.31	0.387	0.129	0.15	29.4%	0.51
10	1100	3080	11.79	7.79	1.39	+2.61	0.349	0.116	—	—	—
11	2000	3080	11.79	8.63	1.39	+1.77	0.306	0.102	—	—	—
						+4.07					

The following diet was eaten during this experiment:—

Days.	9
1-3	4-8
Plasmon	70 gm.
Cocoa	17 gm.
Cream	17 gm.
Egg	450 c.c.
Salt	2
Lactose	10 gm.
	300 gm.
Nitrogen intake	11.89 gm.
Calorie value	1840

TABLE III  
Experiment III. Date, Jan. 2-Jan. 12, 1913.  
(Subject E. P. P.)

Day of Expt.	Body Weight in kilos.	Vol. of Urine c.c.	Calorie Value of Food.	Nitrogen Intake. Grm.	Total N. in Urine. Grm.	Faecal N. Grm.	N Balance. Grm.	Uric Acid. Grm.	Uric Acid N. Grm.	Purin Bases N. Grm.	Total Purins N. Grm.	Acidity of Urine c.c. 10 Acid.	Ammonia N. Grm.	Leucocytes per c.mm. blood.
I	—	1185	3885	11.44	11.61	1.78	-1.85	0.410	0.137	—	—	472	0.71	—
II	—	1829	"	11.44	11.94	1.78	-2.18	0.412	0.137	0.031	0.168	452	0.73	—
III	—	1621	"	11.44	12.06	1.78	-2.40	0.444	0.148	0.018	0.166	368	0.72	—
IV	71.6	1215	"	11.44	11.13	1.78	-1.37	0.442	0.147	0.004	0.151	337	0.70	—
							-7.80							
1	70.8	990	2347	11.44	12.67	0.69	-1.82	0.479	0.159	0.080	0.189	394	0.71	—
2	70.9	994	"	11.44	16.73	0.69	-5.98	0.360	0.120	0.015	0.135	474	0.83	5,600
3	69.6	1534	"	11.44	18.60	0.69	-7.85	0.351	0.117	0.013	0.130	536	1.02	—
4	69.1	1085	"	11.44	15.99	0.69	-5.24	0.333	0.111	0.022	0.133	459	1.06	7,460
5	69.0	1250	"	11.44	16.19	0.69	-5.44	0.309	0.103	0.030	0.133	476	1.19	—
6	68.85	1216	"	11.44	14.87	0.69	-4.12	0.243	0.081	0.030	0.111	457	1.22	16,430
7	—	923	"	11.44	14.88	0.69	-3.53	0.284	0.095	0.061	0.156	403	1.52	—
12	—	—	Mixed diet				-33.98							9,020
13	—	—	"											
18 days later	70.6	—	"											

The following diet was eaten during the first 4 days of the experiment:—  
1230 cal.

Arrowroot	300 gm.
Sugar	75 "
Plasmon	60 "
Eggs	3 "
Cream	429 c.c.
Salt	10 gm.

Calorie value per kilo = 54.3

During the remainder of the experiment the diet remained the same, except that no arrowroot or sugar was eaten. The calorie value per kilo was 34, and the total calorie value was 2347.

days. The average for the first four days was 0.144 grm., and for the last four days was 0.083 grm. nitrogen. From the ninth to the eleventh day 200 grm. of lactose were added to the diet. The uric acid showed some tendency to rise, but it was not very marked, the average output being 0.116 grm. nitrogen.

The absence of any preliminary period on a standard purin-free diet in these experiments, from which the normal endogenous uric acid output can be determined, is unfortunate. But a comparison of the average output for the last four days with that of the first four days shows that a great drop in the uric acid took place. The normal uric acid of this subject on a purin-free diet was determined in Experiment IV, and was 0.175 grm. nitrogen. The average output for the last four days in Experiments I and II was therefore less than half the normal value.

During the preliminary period of Experiment III (subject E. P. P.), when the diet contained protein, fat, and carbohydrate, and was of sufficient calorie value, the uric acid output was very constant and amounted to 0.142 grm. nitrogen, and this figure must be taken as the normal endogenous uric acid output for this subject. On reduction of the calorie value by the withdrawal of the carbohydrates, the uric acid output fell very steadily after the first day. The average output for the first four days was 0.127 grm., and that for the last three days was 0.093 grm. nitrogen. These figures show a considerable reduction in the uric acid output as compared with the output in the preliminary period.

In Experiment III the purin bases were estimated. Considerable variations occurred. There is some tendency noticeable for the amounts excreted to rise during the protein and fat period, when the uric acid fell. However, the amount of the rise was not sufficient to counteract the fall in the uric acid nitrogen, except on the last day, so that the total purins were on the whole diminished as a result of the diet.

The ammonia output was determined in Experiments I and III and was very different in the two individuals. In Experiment I the average output from the second to fourth days was only slightly less than from the fifth to eighth days, i. e. 0.33 grm. to 0.41 grm. In Experiment III the ammonia output was 0.705 grm. on the first day and steadily rose to 1.52 grm. on the seventh day.

The acidity of the urine was determined in Experiment III, but no marked differences were observed.

The acetone bodies were estimated in Experiments I and II. It has been recently shown that acetone is only excreted in the urine in very small amounts, if at all, and that the substance estimated by the Messinger Huppert method is aceto-acetic acid (Hurtley (9)); the results are therefore given in terms of aceto-acetic acid. The amounts of aceto-acetic acid and  $\beta$ -oxybutyric acid excreted are greater in Experiment II than in Experiment I, although the amount of fat eaten was reduced after the third day in Experiment II. With the increase of the total acetone bodies, the percentage of the  $\beta$ -oxybutyric acid rises to 59 per cent. in Experiment II, whereas it was only 43 per cent. in Experiment I.

Plimmer, Dick, and Lieb (15) estimated the uric acid excretion over a



prolonged period on varying diets. Leucocyte counts were also performed, and it was pointed out that there was a parallelism between the number of leucocytes per c.mm. of blood and the amount of uric acid excreted. However, Siven (17), among other observers, has found no parallelism between the leucocyte count and the uric acid output.

When Experiment III was undertaken it was realized that the conditions would be very favourable for testing this point owing to a gradual fall in the uric acid which occurs on this diet. The leucocyte counts were performed first thing in the morning before breakfast, and duplicate determinations were made, except on the first occasion. A Bürker counting chamber was used. Throughout most of the experiment the leucocytes remained at the normal level. On the night of the ninth day of the experiment the subject had a sore throat and felt chilly, symptoms which he has pretty regularly just at the onset of a cold in the head. By the next morning the cold had definitely begun and the leucocyte count was doubled. However, absolutely no effect was produced on the uric acid output. In fact, throughout the experiment there was not the slightest tendency for the leucocyte count to run parallel with the uric acid excretion.

As the diet in these three experiments was very abnormal and the absence of carbohydrates is known to give rise to considerable disturbances of metabolism, a fourth experiment was carried out in which carbohydrates were substituted for the fat of the diet (Table IV, p. 20).

During the first four days of the experiment the standard egg, milk, and cream diet used by Folin (6) for his 'thirty normal urines' was eaten. This diet contains more nitrogen than the plasmon, egg, and cream diet of the previous experiments and plenty of carbohydrate and fat. The body was practically in nitrogen equilibrium during these four days. From the fifth to eighth days the calorie value of the diet was reduced to 2,170 by the removal of the cream, but the diet still contained a little fat (10 grm.).

The reduction of the calorie value of the diet caused the body to lose nitrogen, but the average daily loss was only 3.03 grm. As more nitrogen had been lost in the other experiments, after four days the calorie value of the diet was reduced to 1,110 by substituting plasmon for the eggs and some of the Horlick's Malted Milk, so that the nitrogen intake remained about the same. The average loss for the four days was 5.1 grm. During the last three days of the experiment all the carbohydrate was removed from the diet and fat added in its place. The nitrogen intake remained the same, but the calorie value was raised to 1,330. The diminished protein sparing effect of the fat as compared with carbohydrate was well shown, for, in spite of the increase in the calorie value of 220, the nitrogen loss was increased to 6.4 grm.

The uric acid output during the preliminary period of four days varied from 0.195 grm. nitrogen on the first day to 0.145 grm. on the third day, and the average output was 0.176 grm. nitrogen. From the fifth to the eighth days the average output of uric acid was 0.18 grm. nitrogen; while from the ninth to twelfth days the uric acid was rather higher and the average output was

TABLE IV  
Experiment IV. Date, March 9-24, 1913.  
(Subject G. G.)

Day of Expt.	Weight in kilos.	Vol. of Urine c.c.	Food. Calorie Value.	N. Intake, Grm.	Total N. in Urine, Grm.	N. in Faeces, Grm.	N. Balance, Grm.	Uric Acid, Grm.	Purin Bases, N. Grm.	Total Purins, N. Grm.	Ammonia N. Grm.	Acidity in c.c. of N. Acid, $\frac{10}{10}$	Aceto-acetic Acid Reaction, Rothera's Test.
Period I													
1	67.4	1530	3370	17.6	16.15	—	—	0.586	0.195	—	0.796	558	—
2	—	1340	3370	17.6	16.41	1.54	-0.35	0.533	0.178	—	0.807	605	—
3	—	1330	3370	17.6	16.55	1.54	-0.49	0.44	0.147	0.020	0.769	610	—
4	—	1375	3370	17.6	16.05	1.54	+0.01	0.559	0.186	—	0.784	569	—
Period II													
5	—	1650	2470	16.7	16.99	1.72	-2.01	0.490	0.163	—	0.808	577	—
6	—	1260	2170	16.7	18.35	1.72	-3.37	0.554	0.185	0.030	0.706	630	—
7	—	1610	2170	16.7	18.57	1.72	-3.59	0.587	0.195	—	0.727	620	—
8	—	1350	2070	16.7	18.12	1.72	-3.14	0.529	0.176	0.021	0.746	608	—
Period III													
9	—	1430	1620	15.8	18.62	1.72	-4.54	0.587	0.196	0.016	0.565	464	faint
10	—	1670	1110	16.8	20.79	1.72	-5.71	0.642	0.214	0.020	0.386	250	faint
11	—	1515	1110	16.8	20.58	1.72	-5.5	0.613	0.204	0.014	0.361	265	faint
12	—	1615	1110	16.8	19.87	1.72	-4.79	0.568	0.189	0.018	0.384	262	faint
Period IV													
13	—	1215	1330	17.0	21.6	1.72	-6.3	0.514	0.171	0.016	0.502	429	strong
14	—	1320	1330	17.0	21.9	1.72	-6.6	0.494	0.165	0.025	0.599	473	strong
15	62.0	1230	1330	17.0	21.1	—	—	0.440	0.147	0.032	—	—	—

The following diet was eaten during this experiment:—

Day	1-4	5-8	9-12	13-15
Milk	600 c.c.	600 c.c.	600 c.c.	—
Cream	300 c.c.	—	—	300 c.c.
Horlick's	—	—	—	—
Malted Milk	200 gm.	200 gm.	100 gm.	—
Eggs	9	9	—	—
Sugar	100 gm.	25 gm.	—	—
Plasmon	0	0	105 gm.	140 gm.
Salt	10 gm.	10 gm.	10 gm.	10 gm.
Nitrogen intake	17.6 gm.	16.7 gm.	16.8 gm.	17.0 gm.
Calorie value	3370	2170	1110	1330

0.20 gm. nitrogen. In the last three days of the experiment, when no carbohydrates were eaten, the uric acid showed a definite fall to 0.147 gm. nitrogen and the average output was 0.161 gm. nitrogen.

The experiment shows that when carbohydrates are present the uric acid output does not fall, although the nitrogen loss may be considerable.

Throughout most of this experiment the purin bases were estimated. The amounts excreted were fairly constant, but at the very end of the experiment, when the diet was changed, there was a slight tendency for the output to rise, but the rise was insufficient to compensate for the fall in the uric acid. The total purins were fairly constant, but a slight fall was noticeable during the last three days, which thus resembles the result obtained in Experiment III.

The ammonia output for the first eight days of the diet was very constant, only varying between 0.7 and 0.8 gm. nitrogen. The acidity of the urine also remained very constant during this period and varied from 569 c.c. to 630 c.c. of  $\frac{N}{10}$  acid.

The substitution of the plasmon for the eggs in the third period was followed by a drop in the ammonia output to 0.384 gm., while the acidity was only equivalent to 262 c.c. of  $\frac{N}{10}$  acid. The urine of these days was faintly alkaline to litmus and a faint Rothera's test was present. The removal of the carbohydrates in the last period was followed by a rise in the ammonia output to 0.599 gm. nitrogen and the acidity was equivalent to 473 c.c. of  $\frac{N}{10}$  acid. The change in the ammonia and acidity in the third period is almost certainly due to the addition of plasmon to the diet, as it contains 7 per cent. of ash, while eggs only contain 3 per cent. ash. The rise of the ammonia and acidity in the last period was due to the acidosis produced by the withdrawal of carbohydrates, as the aceto-acetic acid reaction was well marked in the last three days.

Experiments I, II, and III show that when a diet is taken of such a nature as to produce acetone bodies in the urine, there is a diminution in the uric acid excretion. In Experiment IV, where the urine was free from acetone bodies, owing to the presence of carbohydrates in the diet, the uric acid excretion showed no diminution. The question arises as to whether it was the acidosis of the first three experiments which caused the fall in uric acid. However, if a diet of starch and cream is taken, the uric acid excretion also diminishes. There is certainly no production of acetone bodies in this case, but there is the possibility that another type of acidosis occurs, presumably due to the lack of bases in the diet. In two of Folin's experiments on this diet potatoes were eaten on one day instead of arrowroot; on this day the excretion of uric acid was high, and what is also significant, less nitrogen was excreted in the form of ammonia than when the pure starch was eaten. Folin ascribed the rise in uric acid to a special property of the potatoes, and pointed out that in Siven's experiment, where the uric acid remained high in spite of the low protein metabolism, potatoes formed

an important item in the diet. Another explanation was that the high uric acid in these cases was due to there being plenty of bases in the potatoes, as this food when burnt yields an alkaline ash. On this hypothesis the diminution in the uric acid excretion on the starch and cream diet would be due to an acidosis, owing to a lack of bases in the food, and this would agree with the first three experiments of this paper, where there was certainly an acidosis present, and also a fall in the uric acid.

This hypothesis was tested in the following experiment (Table V). After three days on Folin's standard non-purin diet of egg, milk and cream, the starch and cream diet was taken for five days, but varying quantities of sodium bicarbonate were taken in addition (4 to 15 grm.) (Table V, p. 23).

The nitrogen excretion diminished very rapidly, falling from 16 grm. to 4 grm. in three days. Owing to the sodium bicarbonate the urine was alkaline to litmus throughout the experiment. The acidity of the urine to phenol-phthalein was markedly diminished (column 9), and the amount of nitrogen excreted as ammonia and its percentage of the total nitrogen (columns 10 and 11) were much less than Folin and ourselves found when no alkali was taken with this diet. At any rate there does not seem to be any possibility of an acidosis occurring in this experiment.

However, the uric acid excretion (columns 7 and 8) began to diminish as soon as the starch and cream diet was begun, resembling the other experiments, when no sodium bicarbonate was taken.

During the first two days on the egg, milk, and cream diet, the amount of uric acid nitrogen excreted was 0.17 and 0.16 grm., i.e. about the same values as were obtained with this subject in the preliminary period of Experiment III. On taking the starch and cream diet, an uninterrupted fall in the uric acid excretion took place until the fifth day, i.e. a fall of about 40 per cent. As sodium bicarbonate had been taken it is out of the question to attribute this fall to the presence of an acidosis.

On the eighth day two kilogrammes of potatoes were eaten and a little butter. As no cream was taken the calorie value was rather lower than during the rest of the experiment, and to this fact may be attributed the rise in the nitrogen output of 1.6 grm. The uric acid also rose slightly, but this may have been due to the rise in the protein metabolism.

#### *Discussion of Results.*

The experiments just described, and those of the various authors we have mentioned, show that the amount of uric acid excreted on a purin-free diet is not a constant quantity, but varies with the nature of the diet. It is reasonable to try to account for this variation by considering the effect of these diets on the metabolism of the body.

The uric acid excretion is diminished in three conditions:

1. Starvation (observed by several authors).

TABLE V  
Experiment V. May 2-9, 1913.  
(Subject E. P. P.)

Day of Expt.	Body Weight in kilos.	Vol. of Urine c.c.	Food.	Nitrogen Intake. (approx.) Grm.	Total N. in Urine. Grm.	Uric Acid. Grm.	Uric Acid N. Grm.	Acidity c.c. N/10 Acid.	Ammonia N. Grm.	Ammonia N. as a % of total N.
I	—	2032	Folin's egg and milk diet	17.6	17.5	0.51	0.172	598	0.92	5.3
II	—	1462	"	17.6	16.10	0.48	0.16	574	0.79	4.9
1	73.1	1150	Starch and cream + 15 grm. NaHCO <sub>3</sub>	0.4	10.60	0.389	0.139	248	0.34	3.2
2	—	2137	" + 15 grm. NaHCO <sub>3</sub>	0.4	7.17	0.381	0.127	57	0.21	2.9
3	—	1802	" + 3.75 grm. NaHCO <sub>3</sub>	0.4	4.11	0.306	0.102	42	0.17	4.0
4	72.2	1265	" + 7.50 grm. NaHCO <sub>3</sub>	0.4	3.44	0.235	0.098	14	0.18	5.3
5	—	1561	" + 7.50 grm. NaHCO <sub>3</sub>	0.4	3.29	0.294	0.098	40	0.15	4.7
6	70.9	2334	Potatoes 2 kg. and a little butter	—	4.90	0.369	0.123	30	0.22	4.5

On the first two days of the experiment, and on the day immediately preceding, Folin's egg and milk and cream diet was taken, containing 17.6 grm. N. in the day, with a calorie value of approx. 46 per kilo. From 3rd-7th days inclusive, 450 grm. arrowroot and 180 c.c. cream (51 % fat) were taken, with a calorie value of 37.5 per kilo. A varying

quantity of sodium bicarbonate was also taken. On the 8th day potatoes only were eaten, and a little butter. From the 3rd-8th day the urine was alkaline to litmus. There was no glycosuria.

TABLE VI

	N. Intake. Grm.	Carbohydrate Intake. Grm.	Fat Intake. Grm.	Total N. in Urine.	Uric Acid in Urine.	N. Balance. Average per diem for 7 days. Grm.	Acidosis. Rothera's test.
Starvation.	0	0	0	high	low	-12	++
Carbohydrate-Fat diet (starch and cream)	1	600	90	low	low	-4 or 5	0
Protein-Fat diet (Plasmon, egg, and cream). Expts. I, II, III	12	0	150	high	low	-4 or 5 grm.	++
Protein - Carbohydrate diet. Expt. IV, Period III	17	100	27	high	high	-5 grm.	0



2. When a diet of carbohydrate and fat is taken.

3. When a diet of protein and fat and of insufficient calorie value is taken.

The characters of these diets and some of the associated alterations in metabolism are shown in Table VI, p. 23.

Burian and Schur stated that the endogenous uric acid output was constant for any individual, under normal conditions of diet. Siven's experiment showed that the uric acid remained constant when the amount of nitrogen excreted varied within wide limits (3 grm. to 20 grm.). Folin, in direct opposition to Siven, concluded, as a result of six experiments, that the uric acid output was dependent on the amount of protein metabolism, diminishing as the protein metabolism diminished. Our experiments on a similar diet support this observation, but it is obvious that a lessened protein metabolism will not account for the fall in the uric acid output observed in starvation, or in our experiments on a protein and fat diet, for in both these cases the protein metabolism remained high.

There is one factor common to all three conditions associated with a fall in the uric acid, and that factor is protein loss. In eight days the body lost over 34 grm. of nitrogen on the carbohydrate and fat diet; the loss was about the same on the protein and fat diet. In starvation the loss was much greater, i. e. over 50 grm. nitrogen in four days. However, in Experiment IV, when a diet of protein and carbohydrate was eaten, the body sustained a loss of 32 grm. nitrogen in eight days, but no fall in the uric acid excretion took place. Hence it is obvious that mere protein loss cannot be the whole cause of the diminution in the uric acid excretion.

In starvation and on the protein and fat diet an acidosis occurs associated with the presence of acetone bodies in the urine. In Experiment V, on the carbohydrate and fat diet, a fall in the uric acid excretion took place, although the possibility of any acidosis was definitely excluded by the administration of a considerable quantity of sodium bicarbonate. Hence a state of acidosis cannot be the sole cause of the diminution in the amount of uric acid excreted.

In the three conditions, where the uric acid output was diminished, there was probably an increase in the fat metabolism. In starvation and on the protein and fat diet this increase must have been considerable, especially as there was a loss of body weight. On the carbohydrate and fat diet the fat metabolism was almost certainly increased, although there was no direct evidence of it. In Experiment IV on the protein and carbohydrate diet only a little fat was eaten. As the calorie value of the diet was low (only 1,200 from the ninth to the twelfth days), there must have been a considerable consumption of body fat, and this is shown by the loss of body weight. The uric acid, however, remained as high as before. Therefore the increased consumption of fat cannot be the whole cause of the diminution of the uric acid excretion in the other experiments.

It has long been realized that endogenous uric acid normally arises from non-purin compounds by some kinds of synthesis, for a purin-free diet may be taken for long periods without any decrease in the uric acid. A hypothesis that



at any rate agrees with all the conditions shown in Table VI is that the excretion of endogenous uric acid is in part due to its synthesis in the body from protein and carbohydrate.

In any ordinary purin-free diet, such as was used by Burian and Schur, both protein and carbohydrate are plentiful, and the uric acid on this hypothesis would remain at a fairly high level, as is actually the case. If either the protein or carbohydrate metabolism is suddenly reduced, the uric acid formed by their interaction must also diminish, and the output of uric acid in the urine will fall in consequence. This fall actually occurs on the carbohydrate and fat diet, where protein metabolism is much diminished, and it also occurs on the protein and fat diet and during starvation, when the carbohydrate metabolism is rapidly diminished, as is shown by the immediate excretion of acetone bodies, while the protein metabolism remains the whole time at a high level.

Experiment IV was designed to be the converse of the protein and fat experiments. The diet was of similar nature, but plenty of carbohydrates were included and very little fat. In consequence there was no acidosis and no lack of carbohydrates. The uric acid remained high until the last three days, when carbohydrates were completely removed from the diet, and there was an immediate tendency for the uric acid excretion to fall.

There is also some outside evidence for this hypothesis. Knoop and Windaus (11) showed that when freshly dissociated ammonia acts *in vitro* on glucose at room temperature in the presence of sunlight, methyl glyoxal is formed. This uncommon intermediate product, which is capable of condensation, suggests a way for the formation of purin compounds in the body.

It is not suggested on this hypothesis that all the endogenous uric acid excreted in the urine comes from the interaction of carbohydrate and protein in the body, for if this were the case the uric acid would sink nearly to zero when either carbohydrate or protein was much reduced.

The greatest reduction produced by the diets was about 45 per cent., but in some cases it was only 20 or 30 per cent. Some of the normal endogenous uric acid must, therefore, arise in some other way, e.g. from the metabolism of cell nuclei, as has often been suggested before. This portion represents perhaps the general wear and tear in the tissues, and is not affected by the diet given.

*If these two factors are assumed to govern the output of uric acid, the actual purin metabolism in the body can readily be imagined. On a purin-free diet, purins will be formed by synthesis from protein and carbohydrate; some of these purins will be used to supply the constant waste that occurs from the normal wear and tear of cell nuclei, and the remainder will be excreted directly into the urine.*

This hypothesis can be further considered in relation to the conditions in Table VI. The rapidity with which the uric acid output in the urine is diminished would depend on the suddenness with which protein or carbohydrate metabolism was diminished. In starvation the store of available

carbohydrate would be very rapidly used up, and in Cathcart's case the uric acid reached its lowest level on the second day. In our experiments on the protein and fat diets, the body's store of carbohydrates would presumably last a longer time; the uric acid reached its lowest level on the sixth or seventh day.

However, in starvation the uric acid output is still more complicated, because after remaining at a low figure for four days, it then rose steadily and reached its former level on the tenth day (Cathcart (3)). The amount of nitrogen lost during the first four days of starvation was over 50 gm. in this experiment. It is reasonable to imagine that this amount, corresponding to 312 gm. protein, is about as much as the body can lose under physiological conditions; any further loss would mean the onset of a definite pathological condition perhaps associated with a destruction of cell nuclei. Hence the variations in uric acid output in starvation will be due, at first, to the rapid disappearance of available carbohydrate, so that the synthesis of purins will be arrested and only the amount of uric acid formed normally from the metabolism of cell nuclei will be excreted; later on the destruction of cell nuclei will occur, and this will correspond to a rise in the uric acid excretion.

There are, however, certain discrepancies to be considered. The most important is Siven's experiment, when no permanent fall in uric acid occurred, even though the nitrogen excretion varied between 3 and 20 gm. This result may perhaps be due to a personal idiosyncrasy. As has already been pointed out, the fall in uric acid on the carbohydrate and fat diet varies with different people, and in some of Folin's cases was quite small. In these cases, it might be considered that nearly all the synthesized purin goes to repair the waste of nuclear metabolism, and very little appears in the urine.

However, there is another point about a carbohydrate and fat diet that may arise. When the nitrogen metabolism reaches its lowest level, there is still as much as 3 gm. nitrogen being excreted during the day, an amount amply sufficient for the production of only 0.21 gm. uric acid (0.7 gm. nitrogen), which is the amount to which the uric acid output is diminished on this diet. However, the purin metabolism would have to be far more economically carried out than if there were 15 gm. nitrogen available for this purpose. It is quite possible to imagine that if the diminution in protein metabolism occurred only gradually, the body would by gradual adaptation work more economically and continue to synthesize the full normal amount of purin bodies. There are indications that this is the case. In all the experiments, on a carbohydrate and fat diet in which the fall in protein metabolism occurs rapidly, the uric acid in the urine diminishes. In Siven's experiment, where the protein metabolism at first fell rapidly, the uric acid excretion on the first and third days was lower than at any other time during the whole experiment; the uric acid rose again as the diminution in protein metabolism became more gradual.

There are two experiments of Folin's where a mixed purin-free diet of low nitrogen content was eaten. The protein metabolism was diminished very

gradually and reached a low level (3.5 grm.). However, the uric acid output only fell very slightly. The uric acid output in both these subjects showed a marked fall when the protein metabolism was rapidly diminished, i.e. on the starch and cream diet. The gradual diminution of the protein metabolism in the former case may have allowed the body to adapt itself to a more economical form of purin metabolism.

Cathcart (4) has investigated the uric acid output under various conditions. Most of his results agree with the hypothesis just put forward. However, in one experiment, the subject fasted for one day and on the next two days took a pure fat diet; the uric acid nitrogen was 0.08 grm. on the first and 0.04 grm. on the second and third days. The subject then took a diet of protein (casein), bread, and fat for two days. The amount of uric acid suddenly rose to 0.13 grm. and 0.19 grm. on these two days. This sudden rise is in opposition to Experiments I, II, and III of this paper. To test this point further, one of us (G.G.) took a diet for one day of cream only (450 c.c.). The total nitrogen of the urine on this day was 9.5 grm. and the uric acid nitrogen was 0.093 grm. On the next day 80 grm. of plasmon were added to the cream and the total nitrogen of the urine rose to 13.9 grm., but the uric acid was exactly the same as on the day before.

In another experiment of Cathcart, carbohydrates were eaten for five days, and the uric acid remained at the same level throughout. However, in this experiment the diet contained 4 grm. of nitrogen, and the nitrogen in the urine only fell to 4.4 grm., and the fall was much more gradual than in the experiments of Folin and ourselves on the starch and cream diet.

The hypothesis that the uric acid of the urine on a purin-free diet arises partly as the result of a synthesis in the body from carbohydrate and protein, and partly from the wear and tear of nuclear metabolism, agrees with the results of our experiments, and can also be reconciled with the results of other authors, so that for the present, at any rate, it may be regarded as a suitable working hypothesis.

Experiments on the influence of similar diets on patients suffering from gout, together with the estimation of the uric acid in the blood, are being made by one of us.

#### *Conclusions.*

(1) The consumption of a diet consisting of protein and fat of insufficient caloric value causes a fall in the endogenous uric acid output of between 30-50 per cent.

(2) If most of the fat in the previous diet is replaced by carbohydrate, there is no fall in the output of endogenous uric acid.

(3) A fall in the endogenous uric acid is also produced in two other conditions:—

(a) Starvation during the first few days.

(b) The consumption of a carbohydrate and fat diet.

(4) The following possible causes to account for the diminution in the uric acid output have been considered:—

- (a) Diminution in protein metabolism.
- (b) Loss of body protein.
- (c) Acidosis.
- (d) Increased fat metabolism.
- (e) The interaction of protein and carbohydrate metabolism.

There are decided objections to the first four hypotheses; but the last hypothesis seems to agree with the facts observed by other authors and ourselves.

#### APPENDIX.

*Methods.* The determinations were carried out in duplicate.

Total nitrogen of food, urine, and faeces was determined by Kjeldahl's method.

Uric acid was determined by the Ludwig-Salkowski method in Experiments I and II, and by the Folin-Shaffer modification of Hopkins's method in Experiments III, IV, and V.

Purin bases were determined by Kennaway's method A (10).

Ammonia was determined by the Folin method in Experiment I, and by the Formol titration method in Experiments III, IV, and V.

The aceto-acetic acid + acetone were determined by a modified Messinger Huppert method in Experiments I and II.

$\beta$ -oxybutyric acid was determined by the Magnus-Levy extraction method in Experiment I, and by Hurlley's method in Experiment II.

The calorie values were calculated from Atwater and Bryant's tables.

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## REVIEW. URICAEMIA AND GOUT

By I. WALKER HALL

URICAEMIA, or urataemia, is said to occur when the quantity of uric acid which can be obtained from 100 c.c. of blood exceeds 0.8 milligramme. The figures are probably too low, for uric acid up to 1 or 2 mg. per 100 c.c. of blood has been found in normal adults some three to six hours after an average meat breakfast. Larger quantities may be present after an excessive intake of purin-rich foods, during leukaemia (especially under X-ray treatment), before and after the crisis in pneumonia, and in uraemia. Uricaemia as a permanency is a dominant gouty manifestation. When it persists with a purin-free diet, and in the absence of leucocytosis, the term 'endogenous' uricaemia may be applied.

Of late, however, a few reports have been made which tend to throw doubt upon these statements. For instance, His has described the case of a gouty patient with many tophi whose blood did not yield an excess of uric acid. Bloch has examined 200 c.c. of blood taken from a man aged 25 years, who had a typical gouty attack in the big toe: uricaemia was not present. These records suggest that too much emphasis, perhaps, has been laid upon results obtained from the examination of isolated specimens of blood from various individuals. At the same time they serve to indicate the necessity for further estimations. When these are undertaken, they ought to be planned so as to display the relations between the uric acid of the blood and the varying circumstances of daily life. In their absence it is impossible to controvert the contention that gout is associated with a tendency to uricaemia rather than with a permanent uricaemia. Similarly, it is difficult to bring forward evidence which will confirm or refute the view that the gouty uricaemia varies in extent with the progress of the disease. Until this hiatus is removed the search for the underlying cause or causes is considerably hampered.

In connexion with children's ailments an extended knowledge of the blood uric acid may be helpful with regard to the classification of the recently described cases of 'infantile' gout. It may also simplify the current discussion upon these conditions and throw some light upon 'lymphatism' and its secondary effects.

Without these data the views of Comby upon the gouty arthritis of children



cannot gain a wide acceptance, while it is not easy to understand what are the processes at work in the case, related by Fraenkel, of a child 4 years old, who from 2½ years onward suffered from periodic attacks of pain and swelling in the big toe, with enlargement of the tarso-phalangeal joints, slight redness of the skin, and localized sensitiveness. Further, it is difficult to explain the tendency to cutaneous and mucosal inflammations exhibited by the descendants of gouty, diabetic, and arthritic patients (Comby), or the concomitant or consequent lymphatism with asthma, occasional vomitings, defective nervous equilibrium and eosinophilia—a symptom complex which Czerny, Paltauf, and Escherich and Pfaunder place under the headings of ‘exudative diathesis’ or ‘neuro-lymphatismus’. The fact that these children exhibit a purin metabolism similar to that met with in gouty patients is one which Uffenheimer rightly emphasizes, and in itself is a call for further observations.

The quantitative methods available for the determination of uric acid in the blood have precluded much work in this direction, owing to their demands for apparatus and time.

In one method 75–150 c.c. of blood are required; or the plasma of 100 c.c. is poured into 0.5 per cent. sodium fluoride. After the albumin is removed by monopotassium phosphate, the uric acid is precipitated by copper and sodium bisulphite, the copper removed and the uric acid re-precipitated with silver salts: the silver in turn is precipitated and the nitrogen of the filtrate determined by Kjeldahl's process.

In another 10–20 c.c. of blood are necessary. The albumin is removed as in the previous method and the uric acid estimated by Gowland Hopkins's ammonium chloride method or by the Ludwig-Salkowski process.

A third method is that of Folin and Denis. It has many advantages and does not take up much more time than some of the qualitative methods when once the technical difficulties are overcome.

20 c.c. of blood are withdrawn into a wide-mouthed, tared bottle containing 0.1 gramme of finely powdered potassium oxalate. The flask and contents are then weighed. Five times the weight of  $n/100$  acetic acid is heated to boiling. The oxalated blood is poured into the boiling acetic acid solution and the heating continued until the solution has begun again to boil. The mixture is filtered hot. The clear filtrate and wash waters are acidified (0.5 c.c. of 50 per cent. acetic acid) and evaporated to 3 c.c. Five drops of a 3 per cent. silver lactate solution, two drops of magnesia mixture, and 10–15 drops of strong ammonia hydrate are next added. The mixture is centrifugalized. The supernatant fluid is removed. To the residue, five drops of freshly saturated hydrogen sulphide water and one drop of strong hydrochloric acid are added. The tube is placed in a beaker of boiling water for ten minutes in order to remove the hydrogen sulphide. The supernatant fluid is added to 2 c.c. of a solution containing 100 grammes of sodium tungstate and 80 c.c. of 85 per cent. phosphoric acid in 1000 c.c. of water and 10 c.c. of a saturated sodium carbonate solution. The resultant blue solution is then compared with a standard uric acid tungstate



solution and the result obtained by the following formula:  $\frac{20 V}{R W}$  milligrammes of uric acid per 100 grammes blood,

where 20 represents depth in millimetres of standard solution ;

$R$ , the depth of unknown solution ;

$V$ , the volume to which the unknown solution is diluted;

$W$ , the weight of blood taken for the determination.

For qualitative work several methods have been recently worked out. It is expected that they will bring within reach a record of the effects of food, digestion, constipation, drink, exercise, occupation, mental conditions, sex, infancy, childhood, puberty, menopause, acute infections, secondary infections, and vascular lesions, senile and pre-senile, upon the gouty uricaemia. On each of these points hardly any figures exist.

Of the several methods the following deserve consideration :

(a) *Gudzent's and Apolant's dialysis method.* The patient is placed on a purin-free diet for three days. 20 c.c. of blood are then withdrawn from the median basilic vein into a sterile tube containing a small amount of 0.5 per cent. sodium fluoride. The blood, which should not have coagulated, is then placed in a fish-bladder condome. The condome is transferred to a vessel containing 40 c.c. of distilled water and allowed to stand at room temperature for two hours. The dialysate is then removed and acidified (6-10 drops of 10 per cent. HCl). Another 40 c.c. of distilled water is placed in the dialysing vessel and dialysis allowed to continue for another two hours at room temperature. The dialysate is then removed and acidified as before. A further 40 c.c. of water are added and treated in the same manner. The three dialysates, 120 c.c. in all, are then evaporated to dryness on a water-bath or in a beaker or saucepan. To the dry residue a few drops of dilute nitric acid are added and the mixture evaporated to dryness. After cooling, a few drops of ammonia are run in. A purple-red colour indicates the presence of uric acid (murexide test).

(b) *Rothlisberger's silver paper method.* A few drops of blood are collected in a glass tube and allowed to clot. The clear serum, after centrifugalization, is used for the test. The operations are carried on in a dark room, or at night with a red light.

A portion of silver paper prepared by Fink in Genf and Merck in Darmstadt is placed in 1 c.c. of a 15 per cent. pure sodium carbonate solution until the paper has absorbed all the fluid. Two drops of blood serum are then placed on the damp carbonate paper and allowed to remain on the paper in a covered vessel for two minutes. The paper is next transferred to distilled water for 10-15 minutes and then put into ammonia solution (1.3 distilled water) for five minutes. A brown glass flask with a wide neck and a capacity of 100-200 c.c. is recommended for this purpose. The paper is next placed in distilled water, and after remaining there for some hours is dried. If uric acid is present a yellow to brown or dark brown patch results. The method requires further confirmation before being used generally.

Umber's suggestion of an intravenous injection of a solution containing 0.5 gramme uric acid, 1 gramme piperazin, and 30 c.c. distilled water, with subsequent testing of the uric acid content of the blood, has not been employed widely owing to the frequently associated subjective symptoms. It may, however, come into general use in some other form.

Folin has already worked out a few cases and states some of his results. They are perhaps best summarized in the following table, in which the non-protein nitrogen and the urea nitrogen of the blood are also given :

	Uric Acid.	Non-protein Nitrogen.	Urea Nitrogen.
	Milligrammes per 100 grammes of blood.		
1. Rabbit, sheep, horse . . . .	0.05	35	13
2. Cat, ox . . . . .	0.20	63	30
3. Chicken, duck, goose . . . .	4.8	30	8
4. Human, group 1 . . . . .	0.8	36	19
5. Human, group 2 . . . . .	1.5	34	18
6. Human, group 3 . . . . .	2.8	36	19
7. Human, with blood-pressures of 160	2.9	50	33
"      "      "      200	1.2	50	22
"      "      "      220	2.7	40	19
"      "      "      260	3.9	52	20
8. Human, alcoholic . . . . .	1.0	43	29
9. Human, chronic gout . . . . .	3.9	25	13
10. Human, chronic gout . . . . .	4.4	30	15
10 A. Human, chronic gout . . . . .	5.2	20	13
11. Human, lead poisoning . . . . .	4.7	50	31
12. Human, lead poisoning . . . . .	4.8	52	32
13. Human, leukaemia . . . . .	3.1	33	14
14. Human, acute nephritis with arterio-sclerosis . . . . .	2.7	40	19
15. Human, chronic nephritis with arterio-sclerosis . . . . .	2.5	38	19

These results obtained in the course of preliminary work suggest that uric acid in demonstrable quantities is always present in the blood and lymph streams. The quantities vary in different persons, and the figures lend support to the view that there may be groups or families exhibiting similar features. In gout and lead poisoning the uric acid contents are higher, although they are by no means so high as was at one time held. The following example shows what happens when a gouty patient replaces an ordinary by a purin-free diet :

	Uric Acid.	Non-protein Nitrogen.	Urea Nitrogen.
	Milligrammes per 100 grammes of blood.		
Gout with purin dietary	5.5	52	36
Gout with purin-free food	3.4	40	18

The findings may be considered also to indicate that the non-protein nitrogen and the urea nitrogen do not vary with the uric acid content of the blood-stream, and further, that as the urinary uric acid output does not show a permanent increase in gout—rather the reverse—the small increase in the blood may denote the extent of the renal inability to maintain the normal equilibrium. Of course, this is building a high tower on very slender foundations, but an acknowledgement of the position emphasizes the necessity for wide-

spread investigations on these lines, the plea for which is the main object of this review.

*The transport of purins.* The exact form in which the purins circulate in the blood-stream has been much discussed. At one time it was held that the quadriurates and biurates were the most probable combinations; at another, it was contended that the purins were linked up to another organic molecule; to-day, there are many who consider that the sodium monourate is the only possible compound. Recent experiments have demonstrated that uric acid may be separated from the blood by dialysis, and that the biurate is an unstable but soluble salt which is constantly changing into a less soluble type, that is to say, from one isomer to another. Potassium urates must also occur, for the red corpuscles are rich in potassium; there may be small quantities of ammonium and calcium compounds also.

With regard to the views of those who uphold the probability of organic combinations, the dialysing properties of uric acid have to be taken into consideration, for dialysis might still be an effective means of separation even were the whole or a part of the purins in close combination with colloid materials.

Again, the occurrence of isomeric forms of uric acid suggests that isomers of purins and pyrimidins may occur.

The researches of the last few years indicate that the precursors of the blood uric acid are poly- as well as mononucleinates, and that these nucleins may yield a pyrimidin as well as a purin nucleus. When the pyrimidin or purin ring is combined with phosphorus and a sugar it has been termed a nucleotide; when the phosphorus is split off and a purin-sugar compound remains, it has been called a nucleoside. The purin nucleosides are adenosin, guanosin, and inosin. These yield the bases adenin, guanin, and hypoxanthin. The pyrimidin nucleosides are thymine, cytosin, and uracil. The sugar has been identified as *d*-ribose, hence the names purin-ribosid and pyrimidin-ribosid.

The nucleins of the glandular and connective tissues are chiefly tetra-nucleotides. Mononucleotides are also known, and di- and trinucleotides probably exist as well. Polynucleotides have been definitely identified; they contain both purins and pyrimidins, the combination between the molecules being associated with the oxygen and phosphorus of the phosphoric acid.

The ferments which bring about an acceleration of the cleavage of nucleinic substances are nucleinase, guanase, adenase, nucleotidase, and nucleosidase.

The nucleins contained in food are unaffected by gastric juice; the protein portion is split off from the nucleinic acid by the action of the pancreatic ferments, but neither the polynucleotides nor the mononucleotides are affected. The succus entericus with its nucleotidase is the more important digestive ferment so far as regards nucleins; it breaks up the poly- and mononucleotides into nucleosides and phosphoric acid. These nucleosides are, to a large extent, absorbed as such. Bacterial action may, however, result in a further cleavage prior to absorption within the tissues. The ferments required for the further

disintegration of the nucleosides are distributed irregularly, and a transport of half-metabolized nucleotides from one organ to another may form a part of the normal processes of the metabolism of nuclein.

The nucleosides, or their products, do not appear to be utilized in the cellular anabolism of nuclein. The nuclear structures are built up chiefly, if not entirely, from non-protein material. The seat of the anabolism is most probably intranuclear, except as regards the inosinic acid of the muscle cell, which may be extranuclear. During periods of growth, or excessive cellular functions, the intranuclear activities are correspondingly increased. The presence of nucleinase, nucleotidase, and nucleosidase in all tissues suggests that these processes are carried out by each cell itself. The resultant nucleins, nucleotides, and nucleosides call for the further changes of deaminization and oxidation: it is probable that these are carried out in one or more organs only. The liver, especially, has a high functional capacity for this kind of work. However, the oxidation and deaminization is never complete, since purin bases and pyrimidin bases occur side by side in the blood-stream, together with the terminal or almost terminal stage, uric acid. Whether the uric acid undergoes further cleavage is a matter for doubt. At one time it was held widely that about one-half of the formed uric acid was broken down to urea and intermediate products. The application of improved methods for the detection of allantoin in urine has shown, however, that the older figures must be discarded. It is probable that allantoin is practically absent from human urine. As allantoin takes the place of uric acid in the urine of animals whose tissues possess high uricolytic powers, it has been suggested lately that uric acid does not undergo cleavage in human tissues, at least not to any extent. Further support for these views has been recently adduced by Taylor in connexion with some feeding experiments with purin bases.

The purin ring or pyrimidin nucleus, with their numerous receptors for the attachment of other substances, suggest many possibilities for isomerism. It may happen that some of these are produced by one type of cell nucleus, some by another; while it is not beyond ordinary bounds of probability to suggest that, in response to abnormal stimuli or excessive demand, other isomers may be formed. If further investigations yield facts which sustain such an idea, it may be more easy to comprehend the types of the demands which are made upon the renal functions. The circulation of the purins as sodium monourate and its simple extraction by kidney cells seems almost too simple to be true. As a rule, biological processes are much more complex. One of the next stages of research will be the determination of the behaviour of renal tissue to the various purin isomers. This may lead on to the identification of the types of nuclein derivations and their precise cellular origin. Perhaps this in turn may reveal whether there are any differences between the nucleotides of normal and gouty tissues. To this end progress in the technics of the cultivation of tissues *in vitro* may furnish a means for the elucidation of some of these questions.

When the nuclein derivatives enter the blood-stream their solubility

becomes an important factor. Uric acid is taken up by blood serum to the extent of 1 in 1000 parts. Some of the uric acid dissolved in this way may be recovered upon centrifugalization, but a proportion remains behind. The latter moiety may be more firmly bound. Urates, on the other hand, are less soluble, namely, 1 in 40,000 parts of serum. Bechhold and Ziegler state that 50 milligrammes of uric acid may be suspended in 100 c.c. of blood serum: anything over this quantity tends to be deposited. For urates, they found 2.5 milligrammes per 100 c.c. to be the limit of saturation.

Gudzent observed that monosodium urate may exist in two tautomeric forms:

1. The fairly soluble, unstable *lactam* (lactam-urate).
2. The less soluble, more stable *lactim* (lactim-urate).

Directly the lactam-urate was produced it passed gradually into the lactim-urate. The lactim-urate is soluble in an artificial serum whose salts are in a natural concentration, to the extent of 8.3 milligrammes per 100 c.c.

37° C.	Uric Acid.	Monosodium Urate.	
		Lactam-urate.	Lactim-urate.
Serum (inactivated)	1 in 1,100	1 in 40,000	1 in 40,000
Water	1 in 15,500	1 in 469	1 in 710

Still, as Taylor points out, the blood is capable of carrying much more sodium urate than it is usually asked to do. The total amount of endogenous uric acid excreted during twenty-four hours rarely exceeds half a gramme. Taking the total volume of blood at  $3\frac{1}{2}$  litres and the volume passing through the lungs as  $4\frac{1}{2}$  litres per minute, and through the kidneys as 1 litre per minute, and the solubility of lactim-urate as 0.1 grm. per 4,000 c.c. of blood, it would seem that the average daily output of 0.5 grm. could be suspended in the quantity of blood passing through the lungs in five minutes or through the kidneys in twenty minutes. The excretion of purins is not spread, however, evenly over twenty-four hours. It varies with food, exercise, sleep, work, fever, infection, &c. Yet after severe muscular exercise or fever the quantity eliminated is well within the suspension capabilities of the blood-stream. It has also to be remembered that of the purins derived from nuclein catabolism a certain proportion circulates in the lymph spaces and lymphatics. This further reduces the quantity present in the blood-stream at any one time. Again, the lymph-stream probably contains more sodium ions than the blood-stream, and thus may tend to delay the entrance of the nucleins into the blood and diminish the blood content still more.

It has been stated that uric acid disappears from the blood of a gouty patient when he undergoes a certain course at a radium inhalatorium. Gudzent is of the opinion that under the influence of the *D* emanations the change of the lactam into the lactim form is delayed and that uric acid disappears. He states that when a rabbit is placed in a radium emanation chamber sodium urate is



more quickly absorbed by its abdominal membranes than by those of a control animal. Further work may confirm and extend these findings.

*Uricaemia in gout.* In spite of the paucity of observations upon the varying uric acid content of normal and gouty bloods, there are one or two facts which call for discussion. It is generally thought that the blood of a gouty patient contains a super-normal amount of uric acid. The purin excretion, however, remains within physiological limits, except during an acute attack. Still, it has to be admitted that little is known about the uric acid blood content of early or late cases, or how it is influenced by the common actions and habits of everyday life.

Recent observations upon the pharmacology of atophan throw a little light upon the matter.

1. When small quantities of atophan (2-phenylchinolin-4-carbonic acid) are taken by a healthy adult, the total daily endogenous urinary uric acid is raised by 0.1 grm. This increase is most marked during the first twenty-four hours and then falls gradually, reaching the normal output on the third or fourth day.

2. When uric acid is injected intravenously into a normal man, its excretion is spread over several days and the total amount injected fails to reappear in the urine. If the injection is given during a course of atophan, then the uric acid excretion is completed within twenty-four hours and the whole amount injected is duly voided.

3. In a gouty individual the same results are obtained as in 1 and 2.

(Similar results have been recorded when sodium salicylate has been given to vegetarians of five or more years' standing.)

Here is a substance which hastens the removal of uric acid in the healthy and gouty alike. Now it is held by many that the uricaemia of the gouty is, to a great extent, due to defective action on the part of the renal cells. It is stated by Taylor, as late as 1912, that the margin of safety with regard to renal excretion is an exceedingly narrow one; that the kidney excretes uric acid slowly and that its powers are soon overstepped.<sup>1</sup> The gouty renal cells plus atophan, however, appear to excrete the same amount as healthy renal cells plus atophan. All this, however, is rather special pleading for the renal cell. The action of the drug upon the actual production of uric acid or upon the final form in which uric acid is brought to the kidney tubules should also be considered in this regard. The problems are by no means so easy as they appear at first sight. Much work is called for in this direction.

Is there any relation between the extent of the uricaemia and the onset of the acute attacks? The evidence is more general than specific. An increased intake of purin material has sometimes been followed by or associated with an acute attack. The leucocytic destruction which occurs during lobar pneumonia and after the use of Röntgen rays has been found now and then to coincide with

<sup>1</sup> Folin (Int. Med. Congress: Section Chemical Pathology, 1913) showed that 5 grammes of atophan reduced the blood uric acid in gouty patients. He considered that atophan stimulated the kidneys to increased activity, provided there was a high uric acid level in the blood.



an acute outbreak. There is a type of uric acid excretion characteristic of podagra, and atophan shortens the acute stages apparently by inducing an increased uric acid output. On the surface these facts might be regarded as almost conclusive, but it will be remembered that over-eating, over-drinking, trauma, mental disturbances, anger, cold, heat, and bacterial action have also preceded acute outbreaks. Further estimations of the urate content of the blood during the acute attack and under the conditions which are said to induce it are needed. In the absence of these it is difficult to imagine that the uricaemia is responsible for the fever, local inflammations, and general systematic disturbances of the podagra. The urates themselves are practically non-toxic. If further investigations tend to show that in all cases of gout there is a definite uricaemia, the uricaemia will be interpreted as the result of unknown causes and not the cause itself.

Similarly, there is not much evidence as to the relation of the uricaemia to the formation of tophi. Urates are deposited slowly and painlessly in healthy as well as in damaged tissues, and are generally dealt with as foreign bodies by adjacent cells. Cartilage and connective tissues are regarded as favourable seats for tophaceous deposits because of their high sodium content, but it has yet to be explained how it is that these structures are infiltrated less in one individual than in another. Is it that in the one case there are more sodium ions, or is it that the deposition is due to some abnormal purin combinations present in the blood and lymph streams? At present the latter are regarded as passive carriers of the urates. The small purin increase that is known to take place in the blood of the gouty individual cannot surely make all the difference, especially as there is such a considerable margin of solubility still available. As a matter of fact, the purely physico-chemical hypothesis is inadequate to explain the relation between the uricaemia and the tophi. It is possible that, after all, the uricaemia plays little or no part in the depositions, and that these are due to the defective removal of substances resultant from local nuclear activities? The question may be extended further by asking if such substances differ in type from those of normal nuclein metabolism, and so fail to be suspended in the surrounding lymph in such a way as to ensure their entrance into the blood-stream. If these problems could be solved, that of the relation of uricaemia to the aetiological factors would be better defined. Curiously enough, the dose of atophan which suffices to bring about a raised excretion of uric acid also cuts short the acute attack and at the same time brings about a removal of some of the deposited urates. The lessening of the uratic deposits may, of course, be due to the increased flow of serum to the inflamed part. The larger tophi, however, are surrounded by layers of young granulation tissue and phagocytes and peritophal fibrous tissue, and these in turn offer some hindrance to the permeation of serum or drugs.

*The meaning of uricaemia.* The quantity of uric acid compounds in normal human blood is only just demonstrable by ordinary methods. Putting this statement in terms of excretion, it may be said that the kidneys normally secrete uric acid from the blood at a rate which prevents any accumulation of urates in

the circulation. That is to say, the average flow of 1 litre of blood per minute through the kidneys suffices for the supply of urates in a solution whose density is suitable for the activities of the renal cells.

When an adult takes a meal consisting of  $\frac{1}{2}$  lb. of beef and  $\frac{1}{4}$  lb. of sweet-bread, containing about 0.620 gm. purins, the moiety which usually appears in the urine, say 0.300 gm., is not fully excreted until 6 to 10 hours have elapsed. When a similar meal is taken by a gouty individual, the full 0.300 gm. is eliminated, but the rate of output is delayed, some 48 to 72 hours being necessary.

The quantity of purins present in the food does not overstep the solubility of urates in the blood-stream, for once the material is metabolized and ready for removal, the amount of blood passing through the kidney—so far as solubility goes—places the whole amount of purins within the reach of the renal cells in less than twenty-five minutes. It is not yet known how rapidly after the intake the blood uric acid is altered, or whether the food purins appear in the blood as sodium monourate or in organic combination. These links are missing from the chain.

In order to explain the slowness in the excretion of the gouty, the view has been put forward that the renal cells are at fault. It will be shown a little later that such a standpoint is hardly permissible until more evidence has been collected. The suggestion that the delay may be due to a defective, or idiosyncratic, nuclear metabolism, which results in the formation of isomeric purins or incomplete purin combination, and which make greater demands upon the selective activities of the renal cells, merits a similar remark.

If Folin's recent findings are considered with regard to these problems, there is normally 70 milligrammes of uric acid in the entire blood-stream—neglecting the lymphatics and lymph spaces; that is, 2 milligrammes of uric acid per 100 gm. of blood  $\times \frac{3500 \text{ c.c. (total quantity of blood)}}{100}$ . Thus, as about

1 litre of blood passes through the kidney per minute, the whole of the uric acid present could be brought to the kidneys in  $3\frac{1}{2}$  minutes. Now the average total output of the kidneys is 500 milligrammes each twenty-four hours, so that if the blood coming to the kidneys continuously contained the 70 milligrammes, the total daily output could circulate through the kidneys in twenty-five minutes. If the renal cells at once remove all the uric acid and the blood in the renal veins is uric acid free, then the estimations of the uric acid contents of the blood will express in exact terms the extent of the endogenous or exogenous nuclein metabolism; if the renal vein blood is not purin free, then the estimations will fail to yield a true picture of the activities of nuclein exchange. It is quite possible, also, that the purin content of the blood varies in the peripheral, pulmonary, hepatic and osseous streams, and that, while in some parts the purins are being carried to the kidneys for excretion, in others they are being transported from one organ to another for further metabolism.

The data relating to these questions and to the rapidity of the appearance of purins in the blood-stream after food, exercise, infection, fever, &c., are as yet

few in number, but they suggest that the excretion by the kidney is tidal in character and that the blood uric acid has similar characteristics.

If the whole matter be reviewed from the standpoint of disease without regard to these several complexities and Folin's figures be taken as a basis, then there is an average content of 2.5 milligrammes per 100 grammes of blood in acute and chronic nephritis and in arterio-sclerosis. Now in these lesions a considerable portion of renal substance is suspended from function, either temporarily or permanently. In spite of such defect, however, the extraction of uric acid from the blood and its subsequent excretion are practically normal. It seems, therefore, that a comparatively small amount of renal tissue suffices for the elimination of the daily quantity of urinary uric acid.

On the other hand, in gout and lead-poisoning, the blood content is about 4.5 milligrammes per 100 grammes of blood, or an increase of about 50 milligrammes in the total blood-stream at any one moment (an increase from the normal 70 milligrammes to 120 milligrammes). The gouty kidney, *per se*, even when arterio-sclerotic conditions prevail, does not show anything like the amount of cellular damage which occurs in acute or chronic diffuse nephritis. So far, then, as histological appearances are an index of functional capacity, the gouty kidney ought to excrete more freely than the diffuse nephritic kidney. How does this work out in the actual daily life? The average daily endogenous urinary uric acid output of a normal adult is about 0.5 gramme, that of a gouty individual is about 0.45 gramme. The balance of 0.05 gramme—granting that the type and extent of endogenous metabolism is the same in each case—is divided between the uric acid tissue deposits and the tissue accumulations. It has been stated that about 0.01 gramme suffices to cover the amount deposited in the form of tophi each twenty-four hours. The remaining 0.04 gramme augments the amount present in the general blood and lymph streams. The increase is 0.0114 to 0.0118 gramme per litre of blood. In other words, the actual increase of uric acid circulating through the kidneys is about 0.00047 per hour. This seems to be a very trifling difference, especially as it is one of amount and not a type. When increased function is called for in heart, liver, lungs, &c., there is generally a compensatory hypertrophy which, for the time, copes with the demand. Renal hypertrophy also is not unknown. After removal or destruction or atrophy of one kidney, the other undergoes hypertrophy and fulfils the requirements of the nuclein and protein exchanges. This hypertrophy may be permanent or temporary. In the latter case there may be a sudden, or almost sudden, drop in the output which follows. This is not what happens in gout. The uric acid excretion is maintained at a low physiological level to the very end. Compensatory hypertrophy of this kind is not called for in gout. The lesion does not belong to this group of pathological processes.

To appreciate, therefore, the standpoint of those who contend that the accumulation of uric acid in the blood is due to renal inadequacy, it is necessary to postulate the presence of a poison acting upon the renal tubules specifically, since it is difficult to conceive of a poison acting upon the nuclear processes

in such a way as to induce a persistently low, uniform level. With regard to the metabolism of exogenous purins the acceptance of renal inadequacy cannot carry with it the same conception, for a gouty patient excretes an extra intake of purins as completely as a normal individual. The only difference is that the time taken for excretion is a little longer. Even this may be overcome by a simultaneous intake of atophan. The gouty kidney, therefore, is not poisoned beyond compensating for and responding to an extra load. Perhaps the situation may be summed up in the observation that the uricaemia of the gouty is maintained in spite of a fair renal elimination.

To turn to the question of the solubilities of uric acid and urates in the gouty blood. It is now agreed that more uric acid can be dissolved, or suspended, in the blood-stream than has ever been shown to be present in gout. It seems, therefore, that neither chemical nor physico-chemical processes suffice to explain the problem. There must be something more, something vital, biological.

On the other hand, it is not yet clear whether the accumulation of uric acid in the blood-stream is a real one. The increase may be actual and indicative, or it may be simply an apparent increase due to the fact that in one instance the uric acid may be extracted with ease, in another with difficulty. The best of the existing methods for the determination of uric acid in the blood are nearly barbarous in their crudity and intensity. They are almost on a par with the chemical methods of hydrolysing proteins by acids, methods which are very distinct from the cellular disintegration at 37° C. in a medium faintly alkaline.

Again, because it has been demonstrated that uric acid and urates can be extracted from the blood-stream, it does not follow that they circulate as such *in vivo*. The methods available for estimation do not distinguish between the several tautomeric forms, nor do they afford any information as to the associations or combinations of purins or pyrimidins with other substances. The results obtained by these methods do not therefore lead to the identification of the precise types of the purin combinations, and accordingly fail to indicate whether the increase is due to a more active transport of purins from one organ to another for further metabolism or simply to a transport to the kidneys for elimination. How far the increases denote a super-normal nuclein metabolism or an unusual type of nuclein cleavage remains at present undetermined.

If the purin accumulation proves to be a real one, namely, an excess of normally formed and normally bound purin in the blood-stream, it will be necessary to account for this increase by postulating a hyper-normal local or general nuclear activity. The next step will be to investigate the conditions associated with any temporary increase of blood purins and pyrimidins.

At the moment, therefore, it is impossible to apply the recent findings to aetiological problems. The most that can be said is that uricaemia is a result of, and not the cause of acute or chronic gouty processes; that while gout may be due to some intermediate metabolite, or bacterium, or virus, there is as yet

nothing definite to go upon. The contention that gout lowers the general tissue resistance and so opens the way to bacterial infections is so obvious that it need hardly be formulated.

It is a slow progress along the zigzag which leads to the centre of the 'gouty maze', but the researches of the last decade have opened up many new and possible pathways thereto. Further advances, however, wait for progress in chemistry and physics, especially in connexion with fermentative processes. In the meantime there is much to be gained by systematic investigations upon the purin contents of the blood of normal and gouty individuals under varying conditions. Perhaps it is not too much to hope that the uricaemia may be found to be associated with this or that disturbance, habit, or functional change.

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*revised*

## STRYCHNINE IN HEART FAILURE

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STRYCHNINE is widely employed as a rapid heart stimulant. This inquiry was undertaken to obtain evidence as to its immediate effect when given subcutaneously in cases of severe heart failure. The blood-pressure, rate and regularity of pulse, rate of respiration, and general condition were recorded for an hour after each injection. The action of repeated doses was not investigated.

### I. METHODS OF INVESTIGATION.

(a) *Choice of cases.* The fifty patients treated were admitted to the London Hospital during the latter half of 1912. They were examined on admission and approved if they presented symptoms and signs of severe heart failure with or without valvular disease; those with heart failure secondary to pulmonary or renal disease were excluded, as were those with pyrexia. During the above period, the cases being practically consecutive, those with a regular rhythm formed rather more than 50 per cent. of cases admitted for heart failure, those with auricular fibrillation rather less than 50 per cent. We have adopted this division throughout the inquiry. Mackenzie has shown how differently these two groups react to another cardiac remedy, digitalis.

Most of the patients showed orthopnoea and oedema of the legs; all had shortness of breath. The summary of cases appended to this paper indicates the class of case treated. (See Appendix.)

(b) *Apparatus.* Mackenzie's ink polygraph was used to record the pulse and respiration. Only by such means can be recorded the rate and irregularity of the pulse in auricular fibrillation. In cases with a regular rhythm the personal factor in counting pulse and respiration is limited by the use of this instrument.



At the end of each interval of five minutes a tracing was taken from the right wrist for a half to one minute; the rate of pulse and respiration was then calculated from the time marker and written on the strip.

The new mercurial sphygmomanometer<sup>1</sup> devised by Leonard Hill was used to record systolic blood-pressure. It was applied to the left upper arm and a reading taken when the pressure of the armlet caused disappearance of the pulse at the wrist. When this was indefinite a mean was taken between this point and that at which the pulse was again felt as the mercury was allowed to fall. The readings of blood-pressure were taken at the end of each interval of five minutes, immediately after the polygraph tracing.

(c) *Administration of drug.* Strychnine sulphate in a dose of one-fifteenth of a grain ( $\frac{1}{15}$  gr. = 0.0044 grm.) was given subcutaneously in each experiment. Freshly obtained tablets, as supplied by Messrs. Burroughs, Wellcome & Co. to the Hospital, were dissolved in fifteen minims of warm boiled tap-water and injected under the skin of the forearm.

(d) *Plan of experiment.* Before any observations were made the patient was allowed to remain quietly at rest in bed for three to eight hours, and during this period no drugs were administered. Great pains were taken to reduce, as far as possible, the suspicion with which the patient naturally regarded the apparatus. Improvement was not promised; he was simply told that we wished to try whether the medicine was suited to his case or not. Records of the pulse, respiration, and blood-pressure were then made ten minutes, five minutes, and immediately before the injection. After the injection, records were made at the end of each period of five minutes during one hour. This method will be clearly appreciated on reference to the tables.

In the first few experiments continuous tracings were taken for the ten minutes immediately following the injection. As no change was shown, and as two or three minutes usually elapse before the swelling at the site of injection is absorbed, we concluded that it was sufficient to take records every five minutes.

At the end of each experiment suitable questions were asked to decide whether the patients felt any benefit from the injection or not.

(e) *Control experiments.* The last five cases in each series were used as controls. On the day of admission the procedure adopted was exactly similar to that described above, except that 15 minims of pure water (boiled tap-water) replaced the strychnine solution. On the following day an experiment was made with strychnine as in the first twenty cases. Naturally the rate of pulse and respiration was rather lower at the beginning of the experiment on the second day than on the day of admission. (Cf. Tables I-V.)

<sup>1</sup> Made by Hicks, Hatton Garden, London, E.C.

## II. TABLES AND CHARTS.

TABLE I.

*Twenty-five Cases with Regular Rhythm. Blood-pressure after Strychnine.*

mins.:-	Inj. Strychnine gr. $\frac{1}{15}$ .														
	BEFORE.			AFTER.											
	10	5	just	5	10	15	20	25	30	35	40	45	50	55	60
Cases.	(115)	(115)	115	115	115	110	110	110	110	105	110	110	110	110	110
I	(105)	105	(105)	110	105	105	105	105	105	100	105	100	105	100	100
II	(120)	120	(120)	120	120	115	115	120	120	115	115	120	120	115	120
III	170	160	170	170	170	170	160	170	165	170	170	165	165	165	170
IV	125	125	120	120	120	125	120	120	120	120	120	115	115	120	115
V	130	125	130	130	130	130	135	135	130	125	125	130	130	130	125
VI	120	120	120	120	120	115	115	115	115	115	115	115	110	115	115
VII	125	120	125	120	125	120	125	120	120	125	125	125	120	120	125
VIII	165	165	165	165	165	165	160	160	165	160	160	160	160	160	160
IX	165	170	165	165	165	165	160	165	160	165	160	160	160	155	160
X	135	130	130	130	130	130	130	130	130	130	130	130	130	130	130
XI	180	170	175	170	170	160	155	150	150	160	150	155	150	160	150
XII	115	120	115	115	115	115	110	115	110	110	110	110	110	110	110
XIII	170	170	165	170	165	165	165	165	160	160	160	160	165	160	160
XIV	170	160	155	155	155	155	155	155	155	155	150	150	150	150	150
XV	165	160	160	160	160	160	155	155	155	155	155	160	160	155	155
XVI	145	145	145	140	145	145	145	140	135	135	135	130	130	130	130
XVII	140	135	135	135	135	135	135	135	135	135	130	135	130	135	130
XVIII	120	120	120	120	120	115	115	115	115	115	110	110	115	110	115
XIX	110	110	105	110	105	110	110	105	105	105	105	100	105	105	105
XX	95	100	100	100	100	105	100	100	100	95	95	95	95	100	95
XXI	160	150	150	145	145	145	145	140	140	140	140	135	140	135	135
XXII	115	115	115	115	115	110	110	115	115	120	115	115	110	110	110
XXIII	105	110	100	100	100	95	100	105	105	105	100	100	100	100	105
XXIV	125	125	120	120	120	120	115	115	115	115	110	115	115	115	115
XXV	125	125	120	120	120	120	115	115	115	115	110	115	115	115	115
Average	135.6	133.8	133.0	132.8	132.6	131.4	130.0	130.2	129.4	129.6	127.8	128.0	128.0	127.8	127.8

Average before strychnine = 134.1 mm. Hg.

Average after strychnine = 129.6 mm. Hg.

TABLE I A.

*Five Cases controlled. Blood-pressure after Strychnine.*

mins.:-	Inj. Strychnine gr. $\frac{1}{15}$ .														
	BEFORE.			AFTER.											
	10	5	just	5	10	15	20	25	30	35	40	45	50	55	60
Cases.	95	100	100	100	100	105	100	100	100	95	95	95	95	100	95
XXI	160	150	150	145	145	145	145	140	140	140	140	135	140	135	135
XXII	115	115	115	115	115	110	110	115	115	120	115	115	110	110	110
XXIII	105	110	100	100	100	95	100	105	105	105	100	100	100	100	105
XXIV	125	125	120	120	120	120	115	115	115	115	110	115	115	115	115
XXV	125	125	120	120	120	120	115	115	115	115	110	115	115	115	115
Average	120	120	117	116	116	115	114	115	115	115	112	112	112	112	112

Average before strychnine = 119 mm. Hg.

Average after strychnine = 113.8 mm. Hg.

TABLE I B.

*Five Cases controlled. Blood-pressure after Water.*

mins.:-	Inj. aq. pura.														
	BEFORE.			AFTER.											
	10	5	just	5	10	15	20	25	30	35	40	45	50	55	60
Cases.															
XXI A	105	105	110	110	105	105	105	100	100	100	100	95	95	95	95
XXII A	165	170	160	160	160	160	150	150	145	140	140	140	135	135	140
XXIII A	120	120	120	120	120	120	110	110	110	110	115	110	115	115	110
XXIV A	105	100	105	105	105	100	100	100	100	100	100	100	95	95	100
XXV A	120	120	125	120	115	120	115	115	115	115	115	115	115	115	115
Average	123	123	124	123	121	121	116	115	114	113	114	112	111	111	112

Average before water = 123.3 mm. Hg.

Average after water = 115.2 mm. Hg.

TABLE II.

*Twenty-five Cases with Regular Rhythm. Rate of Pulse after Strychnine.*

mins.:-	Inj. Strychnine gr. $\frac{1}{15}$ .														
	BEFORE.				AFTER.										
	10	5	just	5	10	15	20	25	30	35	40	45	50	55	60
Cases.															
I	(118)	117	120	112	110	112	110	112	113	111	112	112	108	120	121
II	102	98	100	100	98	100	94	92	90	89	90	94	94	90	91
III	111	110	115	112	113	110	111	112	110	112	111	111	112	111	111
IV	116	116	114	120	118	118	118	117	116	116	116	116	115	115	117
V	102	99	100	99	98	98	99	97	98	99	96	98	96	95	94
VI	99	99	98	100	99	97	98	95	95	98	96	99	98	96	98
VII	89	85	86	86	82	85	81	82	81	81	78	80	79	80	79
VIII	112	109	108	111	109	111	111	109	113	108	109	110	110	110	110
IX	110	107	104	105	104	101	101	101	100	98	97	98	97	95	96
X	136	129	131	126	128	123	124	123	126	123	122	119	118	121	125
XI	118	122	120	120	116	116	114	119	116	113	118	117	116	116	118
XII	93	90	92	92	90	90	88	88	87	90	91	88	88	89	86
XIII	99	103	102	102	101	101	102	100	101	100	100	101	102	101	101
XIV	115	112	111	111	110	113	112	106	106	108	113	109	109	104	106
XV	124	124	120	117	114	111	112	112	112	117	112	111	115	111	112
XVI	108	109	107	102	103	103	102	100	100	102	104	105	102	105	102
XVII	121	119	116	118	113	117	116	111	112	114	107	113	106	104	104
XVIII	120	122	121	119	117	118	116	117	115	114	114	115	115	114	114
XIX	116	119	119	122	122	120	122	122	122	124	125	121	122	120	125
XX	114	113	114	114	113	114	113	112	114	112	111	116	113	113	115
XXI	95	100	93	94	95	100	95	96	95	93	89	93	93	95	97
XXII	87	89	89	92	88	86	84	86	85	85	86	84	87	85	83
XXIII	96	95	93	94	92	91	89	93	90	91	91	91	89	94	93
XXIV	96	94	96	90	94	92	95	102	96	94	91	91	91	93	99
XXV	103	102	99	100	101	98	99	97	96	94	97	97	96	98	100
Average	108.0	107.3	106.7	106.3	105.1	105.0	104.2	104.0	103.6	103.4	103.0	103.6	102.8	103.0	103.9

Average before strychnine = 107.3 beats per minute.

Average after strychnine = 104.0 beats per minute.

TABLE II A.

*Five Cases controlled. Rate of Pulse after Strychnine.*

mins.:-	Inj. Strychnine gr. $\frac{1}{15}$ .														
	BEFORE.			AFTER.											
	10	5	just	5	10	15	20	25	30	35	40	45	50	55	60
Cases.															
XXI	95	100	93	94	95	100	95	96	95	93	89	93	93	95	97
XXII	87	89	89	92	88	86	84	86	85	85	86	84	87	85	83
XXIII	96	95	93	94	92	91	89	93	90	91	91	91	89	94	93
XXIV	96	94	96	90	94	92	95	102	96	94	91	91	91	93	99
XXV	103	102	99	100	101	98	99	97	96	94	97	97	96	98	100
Average	95.4	96.0	94.0	94.0	94.0	93.4	92.4	94.8	92.4	91.4	90.8	91.2	91.2	93.0	94.4

Average before strychnine = 95.1 beats per minute.

Average after strychnine = 92.7 beats per minute.

TABLE II B.

*Five Cases controlled. Rate of Pulse after Water.*

mins.:-	Inj. aq. pura.														
	BEFORE.			AFTER.											
	10	5	just	5	10	15	20	25	30	35	40	45	50	55	60
Cases.															
XXI A	104	101	103	103	100	99	99	99	100	104	100	102	101	100	96
XXII A	108	105	103	106	99	95	94	94	92	93	96	91	91	94	97
XXIII A	92	92	96	95	89	91	89	90	89	85	90	86	87	91	89
XXIV A	117	110	113	115	111	112	109	110	111	112	103	109	107	107	105
XXV A	108	104	101	100	98	99	99	99	95	97	97	99	97	96	97
Average	105.8	102.6	103.2	103.8	99.4	99.2	98.0	98.4	97.4	98.2	97.2	97.6	96.6	97.6	96.8

Average before water = 103.8 beats per minute.

Average after water = 98.4 beats per minute.

TABLE III.

*Twenty-five Cases with Regular Rhythm. Rate of Respiration after Strychnine.*

mins.:—	Inj. Strychnine gr. $\frac{1}{15}$ .														
	BEFORE.			AFTER.											
	10	5	just	5	10	15	20	25	30	35	40	45	50	55	60
Cases.															
I	(37)	37	37	36	39	35	26	30	38	37	35	34	34	38	37
II	34	23	32	29	24	30	32	36	31	33	22	22	36	30	36
III	30	26	28	29	27	28	30	26	27	28	28	30	28	29	28
IV	30	33	36	32	30	31	35	33	35	36	36	40	33	37	35
V	35	34	35	34	34	35	34	29	32	34	35	32	30	34	33
VI	48	38	46	43	39	39	46	42	45	46	41	36	43	43	41
VII	31	30	34	33	27	28	31	31	33	33	33	29	30	29	32
VIII	25	27	31	25	30	31	30	29	34	31	34	32	34	33	36
IX	31	30	25	32	26	27	24	26	25	25	26	28	25	26	28
X	31	27	30	29	29	27	29	29	28	29	28	27	27	26	29
XI	25	25	24	24	24	22	22	23	24	24	25	23	26	24	28
XII	23	24	26	24	25	22	24	27	26	26	24	26	27	26	22
XIII	16	17	17	16	17	16	17	17	17	17	17	16	18	17	18
XIV	39	35	33	29	32	35	35	32	31	25	33	29	31	28	29
XV	31	31	31	32	33	32	32	30	29	29	29	30	31	31	30
XVI	32	35	37	32	27	32	30	32	32	28	25	23	23	31	20
XVII	39	40	40	43	37	37	35	36	36	40	40	36	35	35	37
XVIII	32	31	34	29	30	32	31	33	29	31	29	32	32	30	29
XIX	43	42	41	40	45	42	42	42	44	46	45	44	44	40	47
XX	56	56	56	51	56	57	53	54	56	55	56	52	49	47	50
XXI	33	36	43	41	41	36	36	39	39	33	38	36	39	34	36
XXII	17	21	23	25	25	23	23	22	20	22	21	22	24	22	21
XXIII	10	18	18	21	23	19	20	18	19	17	21	19	20	27	22
XXIV	27	25	24	23	25	22	25	24	22	18	24	20	19	22	22
XXV	23	24	22	22	22	24	23	23	21	23	22	21	22	23	28
Average	31.2	30.6	32.1	31.0	30.7	30.5	30.6	30.5	31.0	30.6	30.7	29.6	30.4	30.4	31.0

Average before strychnine = 31.3 respirations per minute.

Average after strychnine = 30.6 respirations per minute.

TABLE IIIA.

*Five Cases controlled. Rate of Respiration after Strychnine.*

mins.:—	Inj. Strychnine gr. $\frac{1}{15}$ .														
	BEFORE.			AFTER.											
	10	5	just	5	10	15	20	25	30	35	40	45	50	55	60
Cases.															
XXI	33	36	43	41	41	36	36	39	39	33	38	36	39	34	36
XXII	17	21	23	25	25	23	23	22	20	22	21	22	24	22	21
XXIII	10	18	18	21	23	19	20	18	19	17	21	19	20	27	22
XXIV	27	25	24	23	25	22	25	24	22	18	24	20	19	22	22
XXV	23	24	22	22	22	24	23	23	21	23	22	21	22	23	28
Average	22.0	24.8	26.0	26.4	27.2	24.8	25.4	25.2	24.2	22.6	25.2	23.6	24.8	25.6	25.8

Average before strychnine = 24.3 respirations per minute.

Average after strychnine = 25.1 respirations per minute.

TABLE III B.

*Five Cases controlled. Rate of Respiration after Water.*

mins.:-	Inj. aq. pura.														
	BEFORE.			AFTER.											
	10	5	just	5	10	15	20	25	30	35	40	45	50	55	60
Cases.															
XXI A	48	47	46	45	47	46	46	43	47	47	44	49	46	46	47
XXII A	30	27	31	28	29	28	29	26	28	26	28	25	25	31	26
XXIII A	18	26	25	22	20	18	25	19	21	29	26	24	24	19	23
XXIV A	26	23	23	24	22	25	23	22	24	23	23	24	25	24	22
XXV A	22	23	21	22	22	22	21	24	22	24	21	22	23	21	19
Average	28.8	29.2	29.2	28.2	28.0	27.8	28.8	26.8	28.4	29.8	28.4	28.8	28.6	28.2	27.4

Average before water = 29.1 respirations per minute.

Average after water = 28.3 respirations per minute.

TABLE IV.

*Cases with Auricular Fibrillation. Rate of Pulse after Strychnine.*

mins.:-	Inj. Strychnine gr. $\frac{1}{15}$ .														
	BEFORE.			AFTER.											
	10	5	just	5	10	15	20	25	30	35	40	45	50	55	60
Cases.															
XXVI	(142)	142	142	143	139	150	157	139	146	143	140	140	137	133	135
XXVII	102	101	103	101	98	97	99	102	101	105	102	102	100	102	103
XXVIII	(196)	195	197	198	197	198	199	190	196	191	194	192	192	190	193
XXIX	118	116	118	119	127	117	114	116	115	119	113	114	115	110	116
XXX	108	100	102	102	102	108	101	130	117	106	128	90	95	105	103
XXXI	154	145	140	146	145	142	136	145	140	140	133	146	134	140	140
XXXII	147	147	151	145	140	153	148	147	146	145	148	144	145	142	138
XXXIII	175	159	169	173	164	158	163	170	172	163	156	170	146	151	161
XXXIV	105	103	105	102	103	106	107	106	105	103	100	102	99	100	102
XXXV	139	133	145	137	138	124	134	132	136	141	139	136	131	121	120
XXXVI	144	172	161	156	152	146	165	152	154	161	155	161	157	162	146
XXXVII	127	130	130	131	125	125	127	113	122	110	107	110	107	123	123
XXXVIII	131	130	128	128	129	127	129	125	132	128	130	125	128	129	130
XXXIX	81	88	83	85	87	82	89	87	94	91	92	89	85	90	92
XL	126	118	129	133	132	130	123	114	121	116	113	111	105	117	112
XLI	127	123	125	118	123	120	116	121	124	117	118	121	114	121	126
XLII	116	106	110	115	105	109	113	116	118	114	122	101	103	112	117
XLIII	147	141	148	135	134	139	130	138	140	141	135	137	142	140	134
XLIV	150	147	137	135	138	147	142	146	143	141	143	141	143	133	138
XLV	114	115	106	109	108	112	114	104	109	108	106	103	105	109	107
XLVI	147	137	134	143	124	144	146	141	141	136	144	133	141	140	124
XLVII	104	105	104	93	109	104	108	104	94	95	95	95	92	86	101
XLVIII	111	107	106	104	105	104	102	102	102	100	105	108	102	101	99
XLIX	128	126	133	125	119	135	127	132	132	127	124	133	126	127	133
L	176	169	172	161	156	166	160	157	164	159	166	161	159	163	151
Average	132.6	130.2	131.1	129.5	127.9	129.7	129.9	129.2	130.6	128.0	128.3	126.6	124.1	125.9	125.7

Average before strychnine = 131.3 beats per minute.

Average after strychnine = 127.9 beats per minute.



TABLE IV A.

*Five Cases controlled. Rate of Pulse after Strychnine.*

mins. :—	Inj. Strychnine gr. $\frac{1}{15}$ .														
	BEFORE.			AFTER.											
	10	5	just	5	10	15	20	25	30	35	40	45	50	55	60
Cases.															
XLVI	147	137	134	143	124	144	146	141	141	136	144	133	141	140	124
XLVII	104	105	104	93	109	104	108	104	94	95	95	95	92	86	101
XLVIII	111	107	106	104	105	104	102	102	102	100	105	108	102	101	99
XLIX	128	126	133	125	119	135	127	132	132	127	124	133	126	127	133
L	176	169	172	161	156	166	160	157	164	159	166	161	159	163	151
Average	133.2	128.8	129.8	125.2	122.6	130.6	128.6	127.2	126.6	123.4	126.8	126.0	124.0	123.4	121.6

Average before strychnine = 130.6 beats per minute.

Average after strychnine = 125.5 beats per minute.

TABLE IV B.

*Five Cases controlled. Rate of Pulse after Water.*

mins. :—	Inj. aq. pura.														
	BEFORE.			AFTER.											
	10	5	just	5	10	15	20	25	30	35	40	45	50	55	60
Cases.															
XLVI A	147	143	137	134	131	133	142	126	145	153	154	140	139	131	126
XLVII A	129	121	113	121	132	128	132	126	123	120	130	112	110	124	121
XLVIII A	111	114	116	110	108	103	105	108	107	113	109	111	108	111	112
XLIX A	121	116	124	112	123	121	117	119	110	112	115	108	119	122	114
LA	165	166	166	163	159	157	157	150	146	144	156	155	147	161	155
Average	134.6	132.0	129.2	128.0	130.6	128.4	130.6	125.8	126.2	128.4	132.8	125.2	124.6	129.8	125.6

Average before water = 131.9 beats per minute.

Average after water = 128.0 beats per minute.

TABLE V.

*Cases with Auricular Fibrillation. Rate of Respiration after Strychnine.*

mins. :—	Inj. Strychnine gr. $\frac{1}{15}$ .														
	BEFORE.			AFTER.											
	10	5	just	5	10	15	20	25	30	35	40	45	50	55	60
Cases.															
XXVI	(19)	21	18	17	17	17	19	17	19	18	17	18	18	19	18
XXVII	22	24	20	16	16	14	13	14	14	14	14	15	10	14	11
XXVIII	(34)	34	33	38	32	36	32	34	34	35	34	36	34	35	32
XXIX	16	19	19	18	19	18	18	17	17	17	18	17	17	14	16
XXX	20	24	24	22	22	24	22	23	25	24	25	25	24	24	24
XXXI	30	28	28	25	23	25	23	23	23	23	24	25	23	23	23
XXXII	29	28	28	31	30	33	29	32	31	32	29	34	30	29	31
XXXIII	34	36	35	34	32	31	33	30	30	30	29	30	29	29	29
XXXIV	29	29	30	30	32	32	32	30	30	29	28	28	29	29	28
XXXV	27	25	23	22	20	21	19	18	18	21	22	25	20	17	19
XXXVI	21	23	22	20	22	20	23	21	21	20	21	22	19	18	16
XXXVII	40	41	41	41	38	37	42	40	42	40	41	42	33	40	43
XXXVIII	30	28	30	29	30	32	29	29	26	23	24	25	28	23	26
XXXIX	33	34	34	35	32	31	32	31	32	29	33	29	32	30	33
XL	12	14	12	17	13	15	15	16	15	12	13	12	13	14	14
XLI	30	29	28	27	30	28	21	19	22	21	22	24	22	21	20
XLII	30	27	29	28	23	24	26	28	27	27	26	27	26	24	29
XLIII	30	41	40	33	36	25	33	35	28	40	33	35	38	36	32
XLIV	19	21	27	19	21	17	17	20	18	18	23	27	22	29	22
XLV	22	18	16	17	19	21	20	19	19	16	18	17	19	20	18
XLVI	33	35	34	33	29	31	32	33	32	31	33	31	28	29	30
XLVII	37	37	34	38	34	34	31	29	30	31	29	21	29	30	32
XLVIII	29	30	26	26	28	26	24	23	24	23	25	25	25	24	24
XLIX	21	25	17	20	23	24	24	21	24	24	22	18	21	22	21
L	28	27	26	26	28	26	28	30	29	25	28	31	29	28	26
Average	27.0	27.9	26.9	26.5	26.0	25.7	25.5	25.3	25.2	24.9	25.2	25.6	24.7	24.8	24.7

Average before strychnine = 27.3 respirations per minute.

Average after strychnine = 25.3 respirations per minute.

TABLE V A.

*Five Cases controlled. Rate of Respiration after Strychnine.*

	Inj. Strychnine gr. $\frac{1}{15}$ .															
	BEFORE.			↓	AFTER.											
mins. :—	10	5	just	5	10	15	20	25	30	35	40	45	50	55	60	
Cases.																
XLVI	33	35	34	33	29	31	32	33	32	31	33	31	28	29	30	
XLVII	37	37	34	38	34	34	31	29	30	31	29	21	29	30	32	
XLVIII	29	30	26	26	28	26	24	23	24	23	25	25	25	24	24	
XLIX	21	25	17	20	23	24	24	21	24	24	22	18	21	22	21	
L	28	27	26	26	28	26	28	30	29	25	28	31	29	28	26	
Average	29.6	30.8	27.4	28.6	28.4	28.2	27.8	27.2	27.8	26.8	27.4	25.2	26.4	26.6	26.6	

Average before strychnine = 29.3 respirations per minute.

Average after strychnine = 27.3 resp rations per minute.

TABLE V B.

*Five Cases controlled. Rate of Respiration after Water.*

mins. :-	Inj. aq. pura.															
	BEFORE.			AFTER.												
	10	5	just	5	10	15	20	25	30	35	40	45	50	55	60	
Cases.																
XLVI A	35	34	37	26	30	23	30	35	33	33	34	34	30	33	34	
XLVII A	34	38	37	37	35	36	37	40	33	38	35	37	35	38	39	
XLVIII A	30	27	26	28	26	28	26	26	24	26	27	29	26	26	28	
XLIX A	24	23	22	22	24	21	22	22	21	23	24	22	21	22	23	
LA	27	26	29	24	26	25	26	24	24	24	25	25	23	26	24	
Average	30.0	29.6	30.2	27.4	28.2	26.6	28.2	29.4	27.0	28.8	29.0	29.4	27.0	29.0	29.6	

Average before water = 29.9 respirations per minute.

Average after water = 28.3 respirations per minute.

## CHARTS.

## A. Cases with Regular Rhythm.

Chart I. Effect of strychnine on blood-pressure, rate of pulse, and rate of respiration.

Chart II. Comparative effect of strychnine and water on blood-pressure in cases controlled.

Chart III. Comparative effect of strychnine and water on rate of pulse in cases controlled.

Chart IV. Comparative effect of strychnine and water on rate of respiration in cases controlled.

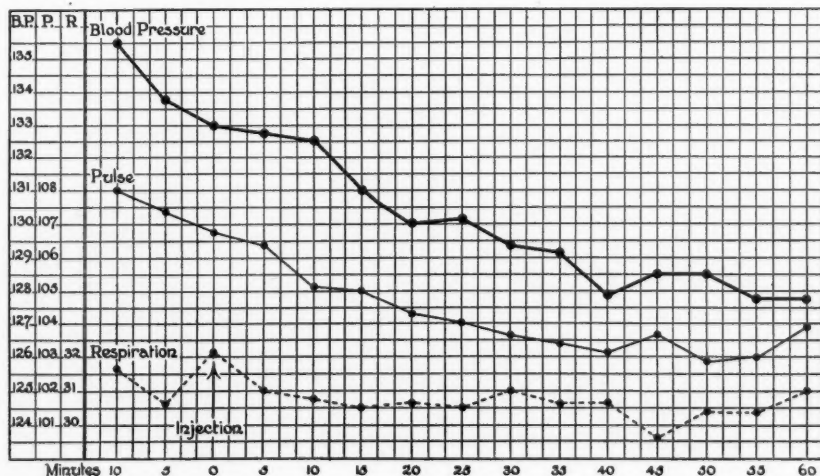
## B. Cases with Auricular Fibrillation.

Chart V. Effect of strychnine on the rate of pulse and rate of respiration.

Chart VI. Comparative effect of strychnine and water on the rate of pulse in cases controlled.

Chart VII. Comparative effect of strychnine and water on the rate of respiration in cases controlled.

CHART I.



E 2

CHART II.

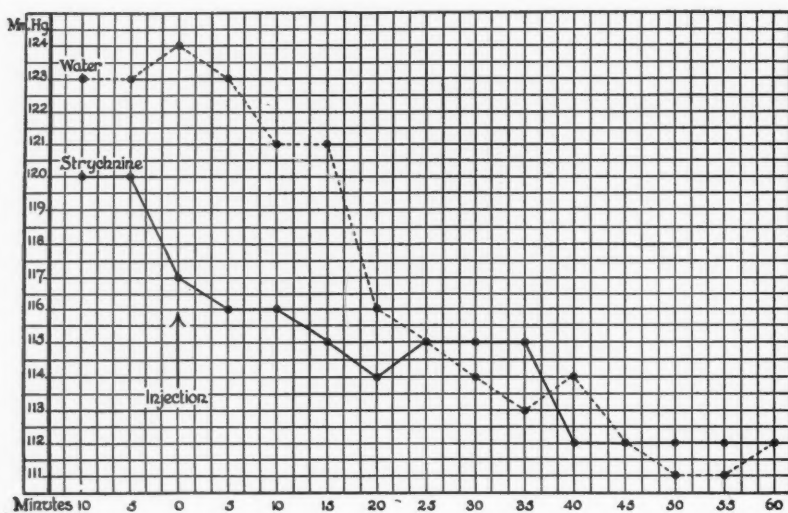


CHART III.

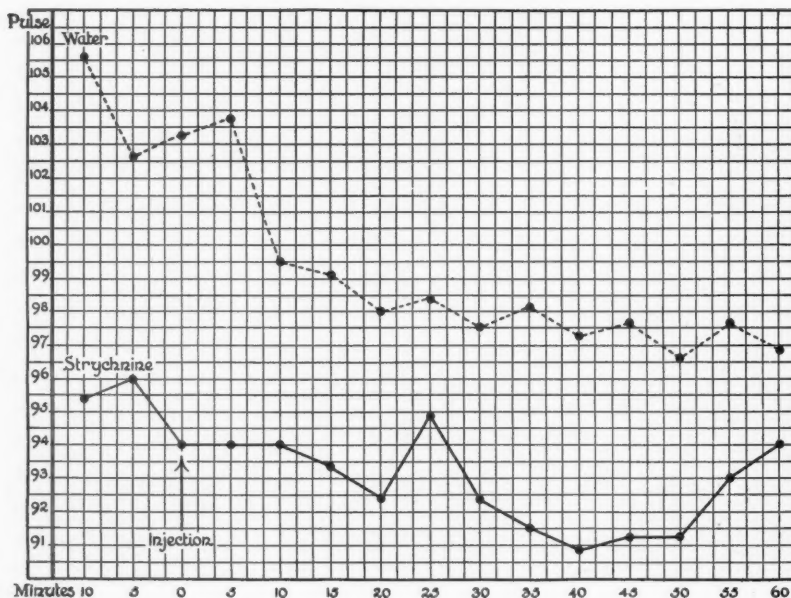


CHART IV.

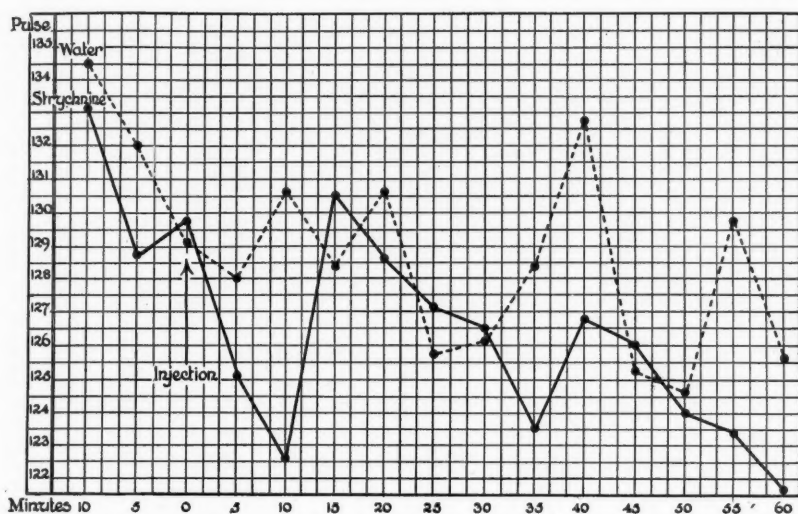


CHART V.

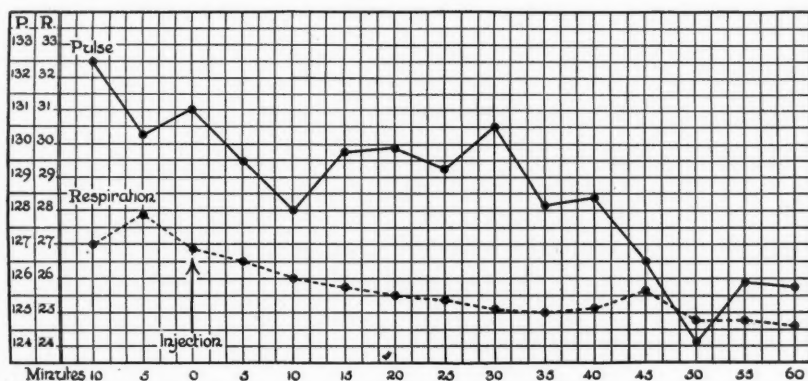


CHART VI.

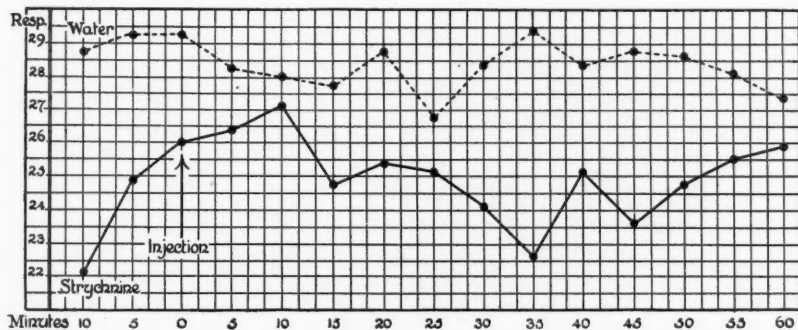
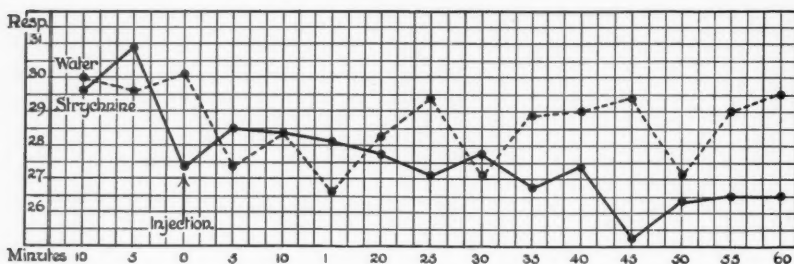


CHART VII.



### III. EFFECT ON SYMPTOMS.

During each experiment a close watch was kept for objective changes in the patients. At the end of the experiment the patients were asked suitable questions to find out whether they themselves had experienced any improvement or not. The inquiry was made casually rather than with solicitude, and leading questions were avoided. Such forms as: 'Have you noticed any change yet?' or 'Do you think you are any better yet or not?' were employed. If a patient claimed improvement, further questions were put to ascertain its nature.

The following were the results of this inquiry as to the effect of strychnine on symptoms:

#### A. CASES WITH REGULAR RHYTHM.

Cases I-VI. None.

Case VII. 'My breathing seems a little bit easier.'

Cases VIII-XIV. None.

Case XV. 'My heart is not beating as much.'

" XVI. None.

" XVII. 'I think I am not so short of breath.'

Cases XVIII-XX. None.

#### *Cases controlled.*

Case XXI (after strychnine). None.

" XXI A (after water). None.

" XXII (after strychnine). 'I feel a bit easier.'

" XXII A (after water). 'I think my breathing is a little easier.'

" XXIII (after strychnine). None.

" XXIII A (after water). 'The pressure over the heart is rather better.'

" XXIV (after strychnine). None.

" XXIV A (after water). None.

" XXV (after strychnine). None.

" XXV A (after water). None.



## B. CASES WITH AURICULAR FIBRILLATION.

Case XXVI. None.

„ XXVII. Experiment 1. None.

„ 2. 'Better in my breathing.'

„ 3. 'My heart is not thumping as much and my breathing is easier.'

Case XXVIII. 'I feel better.'

Cases XXIX-XXX. None.

Case XXXI. Patient thought his breathing was easier.

Cases XXXII-XXXV. None.

Case XXXVI. 'A little better after it.'

Cases XXXVII, XXXVIII. None.

Case XXXIX. Patient thought his breathing was easier.

Cases XL-XLV. None.

*Cases controlled.*

Case XLVI (after strychnine). None.

„ XLVIA (after water). 'Not so tight in chest and my breath is not so hard to get.'

„ XLVII (after strychnine). None.

„ XLVIIA (after water). 'My breathing is much better and my heart is not beating so hard.'

„ XLVIII (after strychnine). None.

„ XLVIII A (after water). None.

„ XLIX (after strychnine). None.

„ XLIX A (after water). 'My heart is a bit quieter.'

„ L (after strychnine). None.

„ LA (after water). None.

## IV. DISCUSSION OF RESULTS.

## A. CASES WITH REGULAR RHYTHM.

1. *Effect on blood-pressure.* Strychnine is usually regarded as a drug which, in therapeutic doses, raises the blood-pressure. We expected to find evidence in support of this current view. A reference to Table I and Chart I shows that *on no occasion was any increase in blood-pressure produced.* The average blood-pressure before the injection was 134.1, after the injection 129.6, a fall of 4.5 mm. Hg. We ascribe the gradual slight fall in blood-pressure and in pulse-rate to an initial rise due to the patients' apprehension of the apparatus, and to the subsequent fall as they became accustomed to the conditions of the experiment.

Tables I A, I B, and Chart II show a similar fall when pure *water* replaced the usual injection of strychnine. Mere rest in bed might also be a subsidiary factor in producing a slight fall even after the preliminary three to eight hours' rest had elapsed.

2. *Effect on pulse.* The average rate of the pulse before injection was 107.6, and after injection 104.0, a slight decrease of 3.3 beats per minute. (See Table II and Chart III.) We ascribe this fall to the same factors as mentioned above under blood-pressure.

It will be seen by reference to the control Tables II A and II B, and Chart III, that the fall happened to be even greater after the injection of pure *water* (5.4 beats per minute) than after the strychnine (2.4 beats per minute).

It was found impossible to get any reliable record of variation in the *volume* of the pulse, if such occurred. A slight change in the position of hand or arm can produce considerable alteration in the apparent volume (height) of the radial beats as recorded on a polygraph tracing. In a few cases the hand was held in one position for some time before and after the injection, but this precaution did not prove satisfactory in overcoming the difficulty. While taking the records of blood-pressure at intervals of five minutes we did not appreciate by touch any increase in the volume of the pulse at the wrist.

In one of the twenty-five cases classed as of 'regular rhythm' premature contractions were present (Case XXII). The premature contractions numbered 4-12 per minute, and this proportion remained unaffected by strychnine. Case VI showed *pulsus alternans* occasionally, both before and after the administration of the drug.

3. *Effect on respiration.* The rate of respiration was unaffected by strychnine (see Tables III, III A, III B, and Charts I and IV). No change in *amplitude* of respiratory movement was noted. Methods of recording the tidal air were not considered applicable.

In four cases out of the twenty-five *Cheyne-Stokes breathing* was recorded on the respiratory tracing. Strychnine had no effect upon this abnormal respiratory rhythm.

4. *Effect on symptoms.* In the first twenty cases slight improvement was acknowledged by three patients (Cases VII, XV, and XVII).

Of the cases controlled (XXI-XXV), one claimed improvement after strychnine, while two claimed improvement after the injection of pure *water*.

In none of this series did we observe any improvement in the condition of a patient.

None of the cases in either series showed twitching or any other sign of poisoning from the injection of strychnine ( $\frac{1}{15}$  gr.).

#### B. CASES WITH AURICULAR FIBRILLATION.

1. *Effect on blood-pressure.* In auricular fibrillation there is such variation in the volume and force of individual beats that it is impossible to obtain any

credible record of blood-pressure by the methods at present applicable to human subjects.

2. *Effect on pulse.* Every beat recorded by the polygraph, however small, was included in the total rate per minute. A graphic record from the apex beat would not have been so generally applicable, nor would it have been a better index of the efficiency of the heart than the record of beats reaching the wrist.

In the twenty-five cases the average rate of the pulse decreased by only 3.4 beats per minute in the hour following the injection (see Table IV and Chart V).

The averages in the control experiments show practically the same fall whether strychnine or water was injected (see Tables IV A, IV B, and Chart VI).

After a close scrutiny of the tracings taken before and after the injection we came to the conclusion that none presented any change in *irregularity*. The tracings both with regard to diastolic periods and amplitude of individual beats seemed exactly the same before and after the strychnine. We obtained no graphic or other evidence that strychnine has any influence on the irregularity of auricular fibrillation.

3. *Effect on respiration.* The average rate of respiration showed a decrease of not more than one or two respirations per minute alike after strychnine and after pure water (see Tables V, V A, V B, and Charts V and VII).

No change was observed in the *amplitude* of respiratory movements, but no exact means were employed for its recognition.

In one case (XLVII) Cheyne-Stokes respiration was recorded; this remained unaffected by the injection.

4. *Effect on symptoms.* In the first twenty cases with auricular fibrillation (XXVI-XLV) four patients acknowledged slight improvement after the strychnine.

One patient (Case XXVII) presented symptoms and signs of severe heart failure for a period of three weeks. An injection was given on three separate days, the first, fourth, and fifth days of observation. On the first occasion there was no subjective improvement. On the second occasion she said she felt better in her breathing. After the third injection she said, 'My heart is not thumping as much and my breathing is easier.' This was said to have been appreciated five minutes after the injection. We noticed that this patient (XXVII) looked better and spoke with greater ease in the third, though no objective change was apparent in the first and second experiments. Case XXXI appeared to have less laboured breathing at the end of the experiment, as he claimed.

Of the five cases controlled, three (XLVI, XLVII, and XLIX) experienced relief after the injection of water and none after the injection of strychnine (XLVI A, XLVII A, XLIX A).

## V. GENERAL CONCLUSIONS.

We found no evidence that the subcutaneous injection of a full dose of strychnine in cases of heart failure with a regular rhythm produces any change in the blood-pressure, rate of pulse, rate of respiration, or general symptoms within the hour following its administration. In cases with auricular fibrillation strychnine produced no change in the rate or irregularity of the pulse, rate of respiration, or general symptoms during the same period.

We conclude that strychnine has no effect which justifies its employment as a rapid cardiac stimulant in cases of heart failure.

We desire to tender our warmest thanks to the Medical Staff of the London Hospital, who generously placed at our disposal all the cases required for this investigation. Dr. James Mackenzie, Professor Leonard Hill, F.R.S., and Dr. Henry Head, F.R.S., gave valued suggestions and advice during the course of the inquiry.

## APPENDIX.

*Summary of Cases.*

## A. CASES WITH REGULAR RHYTHM.

Case I. Bertha H., aged 15. *Mitral stenosis*. Chief symptoms: Dyspnoea. No oedema. Later course: Discharged, little improved, eighteen weeks after admission.

Case II. Ethel M., aged 29. *Myocardial disease; no valvular lesion*. Orthopnoea. Oedema. Died seven weeks after admission. Necropsy.

Case III. Cissie I., aged 36. *Mitral incompetence*. *Pregnancy*. Dyspnoea. Oedema. Discharged, improved, two weeks after admission.

Case IV. George P., aged 56. *Myocardial disease; no valvular lesion*. Orthopnoea. Oedema. Great distress. Died two weeks after admission. Necropsy.

Case V. Laura S., aged 44. *Mitral stenosis*. Dyspnoea. No oedema. Discharged, free from symptoms, six weeks after admission.

Case VI. Charles L., aged 62. *Myocardial disease; no valvular lesion*. Orthopnoea. No oedema. Discharged, improved, eighteen weeks after admission.

Case VII. Joseph C., aged 38. *Aortic incompetence (non-rheumatic)*. Dyspnoea. Oedema. Died one week after admission. Necropsy.

Case VIII. Laura K., aged 22. *Mitral stenosis*. Dyspnoea. Oedema. Discharged, free from symptoms, three weeks after admission.

Case IX. Lewis A., aged 38. *Aortic incompetence (rheumatic)*. Orthopnoea. Oedema: Distress. Sudden death, ten weeks after admission. No necropsy.

Case X. David F., aged 35. *Mitral incompetence*. Orthopnoea. Oedema. Slight cyanosis of ears. Discharged, free from symptoms, eight weeks after admission.

Case XI. Eleanor P., aged 26. *Mitral stenosis*. Dyspnoea. Oedema. Discharged, free from symptoms, four weeks after admission.

Case XII. William C., aged 71. *Aortic incompetence (non-rheumatic)*. Dyspnoea. Cheyne-Stokes respiration. Discharged, slightly improved, two weeks after admission.

Case XIII. John B., aged 30. *Mitral stenosis*. Orthopnoea. Oedema. Discharged, free from symptoms, four weeks after admission.

Case XIV. John D., aged 50. *Aortic incompetence (non-rheumatic)*. Dyspnoea. Gross oedema. Great distress. Death, seven weeks after admission. Necropsy.

Case XV. Ellen Y., aged 39. *Aortic incompetence (non-rheumatic)*. Dyspnoea. Oedema. Improved temporarily; died fourteen weeks after admission. No necropsy.

Case XVI. Samuel B., aged 53. *Aortic incompetence* (non-rheumatic). Dyspnoea. Oedema. Death, two weeks after admission. Necropsy.

Case XVII. Ethel J., aged 22. *Aortic incompetence* (rheumatic). *Mitral stenosis*. Orthopnoea. Oedema. Slowly improved; discharged five weeks after admission.

Case XVIII. Edward P., aged 37. *Mitral incompetence*. Dyspnoea. Oedema. Discharged, free from symptoms, two weeks after admission.

Case XIX. Fred K., aged 18. *Mitral stenosis*. Orthopnoea. Oedema. Great distress. Death, one week after admission. No necropsy.

Case XX. Elizabeth B., aged 48. *Mitral stenosis*. Orthopnoea. Oedema. Death, day following admission. Necropsy.

Case XXI. Ethel S., aged 18. *Mitral stenosis*. Dyspnoea. No oedema. Discharged, improved, three weeks after admission.

Case XXII. Thomas G., aged 47. *Aortic incompetence* (non-rheumatic). *General dilatation of aortic arch* (radiograph). Dyspnoea. Oedema. Discharged, free from symptoms, three weeks after admission.

Case XXIII. Samuel L., aged 59. *Myocardial disease; no valvular lesion*. Dyspnoea. Gross oedema. Discharged, slightly improved, two weeks after admission.

Case XXIV. Clara B., aged 54. *Myocardial disease; no valvular lesion*. Dyspnoea. No oedema. Sudden death, two weeks after admission. No necropsy.

Case XXV. Alice J., aged 35. *Mitral incompetence*. Dyspnoea. No oedema. Discharged, free from symptoms, four weeks after admission.

#### B. CASES WITH AURICULAR FIBRILLATION.

Case XXVI. Joseph W., aged 40. *Mitral stenosis*. *Auricular fibrillation*. Dyspnoea. Jaundice. No oedema. Death, thirteen weeks after admission. No necropsy.

Case XXVII. Rosina A., aged 23. *Mitral stenosis*. *Auricular fibrillation*. Dyspnoea. No oedema. Discharged, improved, fifteen weeks after admission.

Case XXVIII. Leah P., aged 52. *Auricular fibrillation; no valvular lesion*. Dyspnoea. Oedema. Discharged, greatly improved, seven weeks after admission.

Case XXIX. Rose B., aged 40. *Mitral stenosis*. *Auricular fibrillation*. Dyspnoea. Gross oedema. Discharged, improved, four days after admission.

Case XXX. William C., aged 20. *Mitral stenosis*. *Auricular fibrillation*. Orthopnoea. Oedema. Discharged, improved, four weeks after admission.

Case XXXI. Rebecca K., aged 51. *Auricular fibrillation; no valvular lesion*. Orthopnoea. Oedema. Great distress. Discharged, improved, seven weeks after admission.

Case XXXII. Sarah R., aged 47. *Mitral incompetence*. *Auricular fibrillation*. Orthopnoea. No oedema. Discharged, improved, seven weeks after admission.

Case XXXIII. Rachel C., aged 39. *Mitral incompetence*. *Auricular fibrillation*. Dyspnoea. No oedema. Discharged, free from symptoms, three weeks after admission.

Case XXXIV. Catherine C., aged 53. *Mitral stenosis*. *Auricular fibrillation*. Dyspnoea. Gross oedema. Discharged, free from symptoms, seven weeks after admission.

Case XXXV. Annie F., aged 23. *Mitral stenosis*. *Auricular fibrillation*. Orthopnoea. No oedema. Discharged herself, two days after admission.

Case XXXVI. Eliza R., aged 52. *Mitral incompetence*. *Auricular fibrillation*. Dyspnoea. No oedema. Discharged, improved, two weeks after admission.

Case XXXVII. William W., aged 26. *Mitral incompetence*. *Auricular fibrillation*. Orthopnoea. Cyanosis. Oedema. Discharged, free from symptoms, ten weeks after admission.

Case XXXVIII. Eliza R., aged 62. *Auricular fibrillation; no valvular lesion*. Dyspnoea. Oedema. Discharged, improved, nine weeks after admission.

Case XXXIX. Thomas H., aged 58. *Auricular fibrillation; no valvular lesion*. Orthopnoea. Gross oedema. Discharged, improved, five weeks after admission.

Case XL. Sarah S., aged 65. *Mitral stenosis*. *Auricular fibrillation*. Orthopnoea. Oedema. Discharged, improved, four weeks after admission.

Case XLI. Harman B., aged 42. *Auricular fibrillation; no valvular lesion*. Dyspnoea. Oedema. Discharged, free from symptoms, fourteen weeks after admission.

Case XLII. Edward J., aged 56. *Mitral stenosis. Auricular fibrillation.* Dyspnoea. Oedema. Discharged, improved, five weeks after admission.

Case XLIII. Frances S., aged 34. *Mitral stenosis. Auricular fibrillation.* Orthopnoea. Oedema. Sudden death, two weeks after admission. Necropsy.

Case XLIV. Sarah S., aged 52. *Auricular fibrillation; no valvular lesion.* Dyspnoea. Oedema. Discharged, free from symptoms, four weeks after admission.

Case XLV. Emily R., aged 49. *Auricular fibrillation; no valvular lesion.* Dyspnoea. Oedema. Discharged, improved, three weeks after admission.

Case XLVI. Mary D., aged 44. *Mitral stenosis. Auricular fibrillation.* Orthopnoea. Oedema. Discharged, free from symptoms, six weeks after admission.

Case XLVII. James F., aged 59. *Auricular fibrillation; no valvular lesion.* Dyspnoea. No oedema. Discharged, improved, three weeks after admission.

Case XLVIII. Richard W., aged 60. *Mitral incompetence. Auricular fibrillation.* Orthopnoea. Gross oedema. Discharged, free from symptoms, two weeks after admission.

Case XLIX. Mary H., aged 36. *Mitral stenosis. Auricular fibrillation.* Dyspnoea. Oedema. Discharged, improved, eight weeks after admission.

Case L. Annie S., aged 38. *Mitral stenosis. Auricular fibrillation.* Dyspnoea. Oedema. Discharged, greatly improved, twelve weeks after admission.



## ON A TYPE OF CEREBRAL MAL-DEVELOPMENT (FOREBRAIN APLASIA)

By G. A. SUTHERLAND AND HUGH PATERSON

With Plates 3-7

WE desire to draw attention to a peculiar form of cerebral mal-development which produces a characteristic series of symptoms during life and which presents after death definite pathological changes. Our experience is limited to two cases, and we have not read or heard of any others of the same type. As regards the aetiology we can offer no explanation, and for the present assume that there is some defect in the development of the forebrain, dating from an early period of foetal life.

There is nothing in the family history to throw light on the nature of the affection. Both patients were females. Both appeared to be healthy at birth, and attracted attention at the end of the second week by developing 'convulsions', which may be more correctly described as twitching movements. No evidence of any constitutional disease such as syphilis or tuberculosis was discovered either during life or after death.

We believe that an accurate diagnosis can be made during life if the clinical phenomena which are present are carefully observed and studied.

No external evidences of mal-development were seen, and as a matter of fact both infants were rather pleasing and healthy-looking types of babyhood. The heads were rather small, but there was nothing suggestive of a condition of microcephaly. The fontanelle did not pulsate and was not bulging. What was very striking was the curiously apathetic condition in which the child lay, never smiling or looking about, or taking notice of anything. The same placid look of calm indifference was always maintained. It may be said that an infant a fortnight old does not manifest much interest in life generally, but the above description applies to the first six months of life in one case, and nine weeks in the other. No gleam of intelligence was ever present, and no evidence that the child could see or hear. An examination of the eyes showed nystagmus in both cases, but there were no changes in the fundi.

Fits of crying occurred at irregular intervals and would sometimes last for hours. The cry was more like the yapping of a dog, regular, monotonous, weird, expressionless, and invariably of the same nature in the individual patient. The character of the crying suggested an automatic discharge of energy at regular

intervals. At times there was an abortive cry, i.e. the face was screwed up into the expression of crying but no sound was elicited. At rarer intervals screaming of a loud and piercing character was present, but without any sign of pain or distress, and without any obvious cause.

Yawning was a marked feature throughout and of frequent occurrence. Slowly opening its mouth the infant threw its head back, then stretched its limbs, then flexed them—in short, the whole process of a leisurely yawn was gone through.

Sucking and swallowing were seriously interfered with, and this difficulty would appear to increase from week to week. In both cases the history was that for the first few weeks the breast had been taken naturally and satisfactorily, and that later difficulties arose. In hospital the sucking and swallowing were very imperfectly performed at first, and later the infants had to be fed almost entirely by the stomach-tube. In one case the lower jaw was rather firmly fixed at times, and the mouth could be opened only by the use of considerable force.

The respiration was markedly altered. Tachypnoea lasting for hours or days was present in both cases. In one the respirations were counted up to 120 per minute, and in the other up to 160 per minute. While we have met with respirations up to the former rate in connexion with pulmonary disease, we have never seen anything approaching the latter under any conditions. The breathing was always of the so-called medullary type, i.e. superficial, almost purely abdominal, and without any sign of distress. There was no evidence of any pulmonary disease. Tracings of the respiration taken by Mackenzie's ink polygraph showed various cerebral types of breathing. It is to be noted that the breathing of a young infant at rest is normally characterized by various disturbances of the so-called cerebral type. It will be found to be cyclic in character, with periods of active respiration broken by periods of apnoea. The changes found in the cases under consideration were really only an exaggeration of those found under normal conditions. The breathing was often cyclic, spells of active breathing lasting for from nine to thirty-seven seconds, being followed by periods of apnoea, lasting for from four to twelve seconds. The longer the spell of breathing, the longer was the apnoeic period. A long period of respiration usually showed a uniform curve, while the shorter spells were marked by great variation in the depth and rate of breathing. Examples of the various forms of breathing will be found in the accompanying tracings (Plates 4, 5).

Attacks of tachycardia were frequently noted in both patients, the cardiac rate rising to 200 beats per minute. The sounds of the heart at those times were of the foetal character, but no evidence of cardiac disease was detected, and no signs of cardiac weakness (cyanosis, oedema, &c.) were present. Clinically, the cardiac condition was very similar to that seen in paroxysmal tachycardia. The attacks of tachycardia and tachypnoea were sometimes associated and sometimes not.

Pyrexial disturbance was a marked feature in one case, less marked in the other. The temperature would run up suddenly to 104° or 105° F., the skin

would become quite red, and profuse sweating usually occurred. No cause for these attacks could be found on physical examination.

Sensation seemed to be entirely absent. The infants could be placed in any position without discomfort. Neither pinching the skin nor pricking it seemed to produce pain. Stimulation of a limb would at times produce reflex movements, but no evidence of sensation. The fits of crying could not be traced to any local discomfort, nor could they be allayed by any of the usual means.

Twitching of the limbs, which was the first symptom noted in both cases, was a marked feature throughout. Clonic spasms and tonic spasms were present, sometimes continuous for days and sometimes absent for days, but always tending to become more pronounced and more persistent in the form of rigidity. Twitching was less marked in the face than in the limbs. The fixation of the lower jaw in one case has already been referred to. The upper extremities tended to become flexed at the elbows, while the lower limbs were extended at the knees. The feet and hands were often fixed in the position of tetany. Tapping the skull with the finger would sometimes induce immediately a clonic and then a tonic spasm of the trunk and extremities. Opisthotonos was an early and progressive symptom, although at times it passed off altogether, and at other times was very pronounced. Even more striking, because of its rarity in infancy, was a condition of pleurosthotonos which was present in both cases.

These are briefly the chief clinical features which have attracted our notice. As our experience has been limited to two cases there is no doubt that many other symptoms have been overlooked, but they will be supplied in due course by other observers. Taken by themselves, the clinical phenomena suggest an uncontrolled and irregular action of the lower centres of the brain. The absence of consciousness, of sensory impressions, and of all inhibitory influences suggests that the higher brain centres are defective or wanting. These suggestions must be considered in connexion with the post-mortem findings, of which the following is a summary.

#### *Post-mortem Appearances.*

These were so similar in the two cases that a general description of the one applies equally well to the other. On opening the skull and dura mater a quantity of fluid escaped. This was amber coloured in the first case and definitely blood-stained in the other. The amount of fluid was about half a pint, and it occupied the cavity of the pia arachnoid membrane (external hydrocephalus). The arachnoid surface of the dura mater was soft and perhaps slightly thickened (? from deposition of a new layer). In one case there were haemorrhagic patches in the parietal region of the dura.

The brain lying on the base of the skull was very small and covered with thickened, oedematous-looking pia arachnoid, which concealed its outline. The falx cerebri was fully developed and present throughout its whole length. On the removal of the pia arachnoid it was seen that the brain was extremely

ill developed (or atrophied) as regards the cerebral lobes. The atrophy affected the whole of the hemispheres with the exception of the extreme hinder portions of the posterior lobes, which appeared to be normal. The two halves of the dwarfed cerebrum on each side of the falx cerebri were roughly symmetrical, except that in one case a large haemorrhage had taken place into the posterior part of the occipital lobe on the left side, the clot being recent and unorganized.

These represent the pathological changes present, which may be summed up as (1) a very small cerebrum, showing little trace of normal development save in the posterior portion; (2) a large quantity of fluid in the pia arachnoid cavity, which may be regarded as filling up the void left by the shrinking of the cerebrum; and (3) a haemorrhagic tendency in and around the cerebrum, possibly from diminution of normal intracranial pressure.

On the other hand, it was noted that the cerebellum, the medulla, the pons, and the basal ganglia presented a normal appearance. All the cranial nerves could be identified and the blood supply and blood-vessels were normal, so far as could be determined. The lateral ventricles were not dilated, the foramen of Monro was patent and normal, the third and fourth ventricles were not enlarged, and the patency of the iter was established.

Microscopic examination of the pia arachnoid showed that the thickening was probably due to oedema, as the layers were separated save for some junctional strands of connective tissue. There was an excess of cellular elements, some of the lymphocytic type, but the majority probably of fibro-vascular origin. The cerebral substance was very irregular. In places there was a fairly firm tissue composed of fine fibrils which seemed to be neuroglial, and in other places it was more coarsely reticular with glial cells in the loose meshwork. This ground tissue was best developed under the pia mater and around the vessels, but certain sections showed considerable areas of it. There were found in this tissue numbers of large neuroglial cells of the Deiters's type; similar cells were present in the looser tissue, and in addition other cells of the granular type (Körnchenzellen). Relatively few and poorly developed cells could be seen in the superficial layer of the cortex, immediately under the pia mater; they were scarcely past that stage of development in which it is difficult to distinguish them from glial cells. The cortex was everywhere irregularly developed, and no definite lamination was visible. There was also in places an ingrowth of connective-tissue strands into the brain (probably from the meninges) and the blood-vessels were too large, too numerous, and too thick as regards their walls.

Summing up the results of examination of the brain, it may be said that only the portions developed from the anterior vesicle (prosencephalon) were *primarily* affected. The affection of the optic thalamus, &c., was probably only secondary. The fact that the optic nerves, the chiasma and tracts, and the eyes were normal shows that the disease spared the second vesicle (thalamencephalon) or involved it only after the optic vesicles were given off.

Two views may be held as to the meaning of the pathological findings: (1) That there had been a pachymeningitis, with proliferation of the meningo-

vascular tissue, and secondary cerebral involvement. Against this is the fact that there was no evidence of inflammatory changes in the meninges. (2) That there was a primary aplasia of the cerebral tissue with secondary meningo-vascular proliferation. This view is supported by Dr. Gordon Holmes, to whom we have submitted one of the specimens and sections, and to whom we are greatly indebted for a report on the minute anatomy of the brain which has been given in abstract above. As the view which we had formed on clinical grounds, and on the macroscopic appearances of the brain after death, has been supported by Dr. Holmes on the evidence supplied by microscopic examination of the nervous tissues involved, we suggest the term 'forebrain aplasia' for this type of disease.

In considering the diagnosis during life the other possibilities which may present themselves are (1) chronic tetanus neonatorum, (2) meningeal haemorrhage at birth, and (3) congenital internal hydrocephalus. The first of these may be very closely simulated, as in one of our cases. From a consideration of the clinical features described above it will be possible to make a differential diagnosis without much difficulty.

A case has been recorded recently by H. D. Rolleston and Salusbury Trevor (1) in which the clinical symptoms during life were in many respects very similar to those described above. The autopsy in this case showed extensive cystic degeneration of the cerebrum and cerebellum, and other pathological changes which were entirely different from those in the type of disease under consideration.

#### *Two Cases of Forebrain Aplasia.*

*Case I.* E. D. T., female, aged 7 weeks. Admitted October 1907, died March 1908.

*History.* Patient was a full-time child and was perfectly healthy at birth. The labour was instrumental, but there were no external injuries noticed. The cord was attended to in the usual way, there was no suppuration, and it came away on the seventh day, leaving a perfectly healthy scar. The child progressed favourably and took the breast well until the fourteenth day, when it started to have convulsions and passed from one into another with only a minute's interval between.

*Nature of Fits.* The head was suddenly thrown back, the neck and limbs became rigid, the right arm was flexed at the elbow. The back was not noticed to be arched, but the chest was thrown well forward. These fits continued day and night for three weeks. The baby refused to take the breast and spoon-feeding had to be resorted to. The mouth opened well and the child was quite able to swallow. During the fits the child cried almost continually, but there was nothing peculiar about the cry. When a convulsion started the child yawned frequently and stretched herself. There was no vomiting, no sweating, no feverishness; the bowels, however, became very constipated.

The child began to lose weight. Two days after convulsions started, a yellow discharge was noticed coming from the vagina; it had a bad smell and was abundant, causing redness of the parts round about; no rash. The mother bathed the external genitals with warm water and in a week's time the discharge had stopped. No squint was noticed, nor was there any twitching of the face



during the fits. The spasms were always tonic in nature. No discharges from the ears, nose, or mouth. No sores about these parts.

The fits now ceased entirely for two weeks, but started again, although not so frequent as before. It was now noticed for the first time that the jaw became tightly closed, and difficulty was found in opening it; the child also had some difficulty in swallowing. With the return of the fits the vaginal discharge reappeared. The cry was now more a scream. The fits were exactly the same as the first. Three days before admission to Hospital the child screamed out a great deal, the head became retracted, and there was some opisthotonos. The bowels became very constipated.

*Family History.* Father alive and well. Mother alive and well. No other children. One miscarriage.

*Progress.* Oct. 4. There is extreme head retraction and opisthotonos, the child being bent like a bow; the chest is protruded and the shoulders braced back. There is marked general rigidity. The elbows are flexed and the arms approximated to the sides; the legs are extended, and the feet are in the position of equino-varus. On account of the rigidity no knee-jerks can be elicited. Tache cérébrale is present. The child is in a semi-conscious condition, unable to swallow properly and requiring to be fed by means of the stomach-tube. It cries out a good deal. There is a vaginal discharge which contains many pus cells and organisms, some deeply staining diplococci, none however being intracellular. Lumber puncture performed, but no cerebro-spinal fluid obtained.

Oct. 16. The rigidity is not so marked. There is right-sided pleurosthotonos present; the temperature has gone up considerably, having been as high as 103.4°. There has been no vomiting. The eyes have been examined; both discs are pale, especially the left, but there are no indications of optic neuritis or atrophy. Lumber puncture again performed, but no fluid obtained.

Oct. 28. The child lies in a semi-conscious and placid condition. Screaming attacks occur frequently and the cry is loud and piercing in character. The breathing has been a marked feature since admission, is often very rapid, the respiration running up to as many as 112 per minute. There is no dyspnoea and no exaggerated costal action, the breathing being for the most part diaphragmatic. On tapping the skull with the finger there is a flexor response in both upper and lower extremities. Has vomited for the first time since admission.

Nov. 1. The breathing is still very rapid and is irregular at times. Right-sided pleurosthotonos still present at intervals. There is flexor contraction of the right arm, and contraction with extension of the left. Fits are not so frequent. The patient yawns frequently. When the child was uncovered to-day the right arm went into clonic spasm. This soon ceased, but on tapping the skull the arm was again thrown into clonus, the right foot became dorsiflexed and rotated inwards, and went into clonic spasm. The right hand is kept flexed and the fist is closed over the thumb, but when clonus starts the hand opens and fingers take on clonus.

Nov. 15. Potassium bromide (24 gr. per diem) has made the child much quieter. The pleurosthotonos and opisthotonos have disappeared, but the limbs still remain rigid. Has made an attempt to take the bottle.

Nov. 21. The child has been distinctly less rigid during the last few days. The limbs can be flexed on themselves and on the trunk. Head retraction has gone and even the rigidity of the neck is intermittent. The yawning is still a marked feature and is of frequent occurrence.

The rapid diaphragmatic breathing has slowed down to 60 per minute. The crying has been much less of late and might be described as being like the cry of a 'speaking doll'. The pharyngeal reflex is sluggish. The child does not smile or look about. At times there has been slight twitching about the angles of the



mouth and eyes, but no persistent spasm and no risus sardonicus. No definite trismus, but the lower jaw seems rather firmly elevated. No sucking effort on putting the fingers in the mouth. There has been a great deal of sweating of late, the temperature reaching  $105.4^{\circ}$ , the pulse 200, and the respirations 120 per minute. When the temperature was high the child was in a state of rigid spasm, both arms being extended, but there was no head retraction or opisthotonos. Child is coughing a great deal now, but there is nothing to be made out in the chest.

*Nov. 27.* The rigidity is more marked again and pleurosthotonos is present. The rigidity is so great that the limbs cannot be flexed. The pulse is rapid (200 per minute) and child sweats freely. It still requires to be fed by tube. Child does not cry so much now. The breathing at times is irregular, at other times cyclic in character.

*Dec. 4.* Rigidity is still a marked feature, more corkscrew opisthotonos, head and eyes deviated to the right usually. The abdomen and lower chest project. The cry is strong and there is more of the laryngeal element present; it is the same doll-like squeaky automatic discharge as before. The reflex spasm is not so marked on tapping the skull. 10 c.c. of anti-tetanic serum were given on two consecutive days. Pleurosthotonos increased again. Still yawning a great deal.

*Dec. 14.* During the last few days the condition has been more satisfactory. Rigidity and pleurosthotonos have varied in degree. Quite unable to swallow. Still yawning. No results from anti-tetanic serum. Pulse at times becomes weak.

Attempted once or twice to take bottle and on one or two occasions managed quite well. The weight is steadily increasing.

*Jan. 4.* Baby getting fatter daily. Still absence of intelligence and sucking power. Same jerky cry present. Rigidity at times has been absent. Reflex excitability on tapping skull. Temperature has been irregular. On crying opisthotonos is increased.

*Jan. 24.* Opisthotonos and pleurosthotonos still present and both exaggerated when child cries. Child is very rigid and is again quite unable to swallow. Still yawning. Has been sick on several occasions lately. Is very pale; breathing is still rapid, but there is no air hunger. There is again a facial expression of crying, but no noise accompanying it. Conjugate deviation of the eyes and lateral nystagmus.

*Feb. 3.* Rigidity has gone. Still fed by stomach-tube. This afternoon the pulse became very rapid (200 per minute). Temperature  $106.4^{\circ}$ , muscles quite flaccid. Child's condition remained unchanged, and she died at 8.30 p.m.

#### *Post-mortem Examination.*

All the muscles were rigid (dead 20 hours), and the knees were hyper-extended. Thorax and abdomen were normal.

*Skull.* There was a curious condition of the skull, due apparently to the child having lain mainly on the right side. The right parietal bone was depressed below the left and also below the occipital; union had taken place in this position and the projecting edges of these bones had become rounded off. There was asymmetry of the skull due to the same cause.

On cutting into the dura a large quantity of amber-coloured fluid escaped. The dura was found to be thickened (about  $\frac{1}{16}$  in.) and apparently there was a general thickening of the membrane, and also a deposition of a new membrane, of a pink colour and extremely soft, on the inner surface. The process was apparently universal but differed in different places. It was perhaps most

marked over the right parietal region, where the membrane was thicker than elsewhere and showed traces of haemorrhage, but it was also quite obvious in the dura over the parietal plates. Except for the condition mentioned, there was no formation of laminated false membrane and no haemorrhages.

The brain was extremely atrophied, leaving a space between it and the dura, which was filled with fluid. This atrophy affected the whole of the hemispheres with the exception of the extreme hinder portions of the posterior lobes, which appeared normal. The basal ganglia, pons, medulla, and cerebellum appeared normal.

The shrinkage of the cerebrum was extreme and the pia arachnoid was thrown into folds, not having shrunk proportionately. This gave rise to a sort of waxy appearance, the cerebral surface not being clearly seen. The cerebral substance itself seemed to be a very thin layer, or series of thin layers, and gave one the impression that the atrophy affected the deeper portions rather than those immediately beneath the pia. The colour was a dirty grey, and the whole appeared sodden and watery. The ventricles, if anything, were dilated, although it was difficult to make this out exactly in view of the flabby condition of the parts. They contained clear yellow fluid.

No further dissection was made. The cord did not appear atrophic.

*Case II.* F. G., female, aged 5 weeks. Admitted Oct. 30, 1912; died Nov. 28, 1912.

*History.* Child was born at full time, and was breast fed for a fortnight, when she had some convulsions lasting off and on for six days. The breast was stopped and the child was fed on Nestlé's milk. She remained quite well until the night before admission, when she was 'snuffling' a great deal and had difficulty in breathing. At 3 a.m. this morning child was given a bottle, but vomited immediately after it. Went to sleep again, but vomited three hours later; she became very feverish, and there was difficulty in breathing.

*Family History.* Father alive and well, aged 27 years. Mother alive and well, aged 20 years. No other children. No miscarriages.

*On admission.* Body fairly well nourished. The child was breathing in a cerebral fashion, long pauses followed by bouts of extremely rapid respirations, viz. 160 per minute, pulse also quick, i.e. 184 per minute. No lesion in the heart or lungs. Abdomen normal. Well-marked nystagmus. Head well formed, fontanelle open but not pulsating.

*Progress.* Nov. 1. Child will not take bottle and has to be tube-fed. Lies in a completely apathetic condition, without smiling or taking notice when awake. Sleeps chiefly. Can be roused by touching or moving the body, when trunk and limb movements are developed. Insensible to pin-pricks. Has fits of crying, these commencing and ceasing abruptly without obvious cause. Varying condition of rigidity of limbs, extension chiefly with condition of tetany in hands and feet. Knee-jerks present. The respiration is of a most irregular type. The cardiac rate varies much but action is regular.

Nov. 6. Breathing quiet, of cyclic type. Heart rate has fallen to 120 per minute. Child takes no notice and apparently does not see. No effort made to suck or swallow. Is being fed alternately with spoon and stomach-tube. The irregular breathing is still a well-marked feature. It is superficial and abdominal as a rule, with occasional deeper respirations and more of the costal action. Occasional twitchings of both hands and feet and to a slighter extent about face occur, but there has been no definite convulsive seizure. Still has periodical crying fits without apparent cause, which cannot be soothed by ordinary measures. There is now marked head retraction with some opisthotonos. No optic neuritis or other fundal changes.

Nov. 10. The tetany of the hands and feet is still marked, and also head retraction and opisthotonos. Cry is weaker, and child is still unable to swallow. Has occasional yawning turns; the mouth is open and limbs are stretched out in a leisurely manner. There has been some slight twitching on the left side of the face. Still being fed by means of tube. Lumbar puncture performed, but only a few drops of blood obtained. The opisthotonos is now accompanied by a slight degree of pleurosthotonos. The rigidity of the limbs is most marked.

Nov. 15. Opisthotonos is extreme. The right hand is swollen and is of a reddish-blue colour (tetany). The child performs slow rhythmical stretching movements, at the end of which she yawns. The breathing is slower (132 per minute), but is still irregular at times. There is marked facial irritability. The bowels are normal and there has been no sickness. Has made a very slight effort to swallow. Wassermann reaction done and found to be negative. Still yawning a good deal. Head retraction and rigidity of limbs are very great. Breathing still is irregular. Hands pronated and drawn up. Has gained 4 oz. Sensation absent.

Nov. 20. Temperature has been subnormal for the last few days. Bowels constipated. Opisthotonos well marked, also some pleurosthotonos. Tapping on skull still produces a hollow sound, also some twitching movements. Child has lost 10 oz. in weight. Fontanelle is rather depressed; no pulsation can be felt in it. Still some twitching movements of hands and arms. Has a well-marked grunt just at the end of expiration.

Nov. 25. The breathing is quiet again and more regular. Child sleeping peacefully. The bowels are rather constipated. Still a great deal of twitching; this affects both hands and arms, and to a lesser degree the left lower limb. Opisthotonos is very marked. The leisurely stretching movements continue, likewise the yawning. No attempt made to swallow. No sickness. The child has gained a little in weight again. Temperature is swinging slightly. The face at times is very flushed and child sweats a good deal. The breathing is inclined to be jerky.

Nov. 27. Temperature has fallen to subnormal again. Still some twitching present. The opisthotonos is not so great, in fact at times child lies quite straight. Cries out if any part of the body be flicked with the finger. Still no attempt is being made to suck or swallow. The abdomen is rather distended, and a green, offensive motion has been passed. Still yawning and stretching herself at intervals. Some bronchial breathing present at right base.

Nov. 28, 10 a.m. Bronchial breathing and dullness are both well marked at right base this morning. Breathing is quicker and very irregular. No twitching noticed. Rigidity not so marked. Still yawning. Is extremely pale. Died 11.15 a.m.

*Post-mortem Examination. Report by Dr. H. W. Perkins.*

The head resembled that of a normally developed infant of this age, the circumference being  $13\frac{1}{2}$  in. From ear to ear over the vertex the distance was  $8\frac{1}{2}$  in. There was no evidence of any injury to the skull. The anterior fontanelle was widely open, measuring 2 in. in the sagittal direction and 1 in. in the coronal. The sutures were not united. On opening the skull a quantity of blood-stained fluid, amounting to 9 oz., escaped. On centrifugalizing this the blood-cells were thrown down, leaving a clear supernatant fluid of straw colour.

The dura mater appeared normal and the falx cerebri was fully developed

and present throughout its whole length. The haemorrhagic fluid was apparently in the cavity of arachnoid. This cavity was partially divided in the occipital region by a few fine, cobweb-like adhesions, which were chiefly present on the left side. The brain, lying on the base of the skull, was very small and covered with thickened, oedematous-looking pia arachnoid which concealed its outline.

On the removal of this membrane it was seen that the brain was extremely ill developed as regards the cerebral lobes. The brain weighed 80 grammes. Each cerebral hemisphere measured 9 cm. in length, 6 cm. in width, and 3.7 cm. in depth, taking the maximum measurements. The tentorium presented a normal appearance and there was no excess of fluid beneath it.

The two halves of the dwarfed cerebrum on each side of the falx cerebri were roughly symmetrical, except that posteriorly into the occipital lobe on the left side a large haemorrhage had taken place, the clot being recent and unorganized. The middle third of the cerebral cortex on each side presented numerous convolutions, which, although small and narrow, were separated by well-defined sulci. At the anterior poles on both sides the cortex was extremely thinned, and so intimately associated with the pia arachnoid that it was difficult to recognize any well-marked convolutions or sulci. The appearance here was that of numerous small cavities, like a honeycomb, bounded externally by the thinned cortex and pia arachnoid. Definite convolutions and sulci were present at the posterior pole on the right side, but intervening between this and the middle third of the cortex was an ill-developed area having a crinkled appearance, but showing no obvious convolutions or sulci. The posterior pole on the left side was the seat of the extensive haemorrhage referred to previously.

This haemorrhage formed a roughly spherical clot about 25 mm. in diameter, and limited externally by the thinned-out cortex and pia mater; its appearance suggesting the possibility of its having arisen from bleeding into a thin-walled cyst. There were no well-defined convolutions or sulci on the basal surface of the cerebral lobes.

The cerebellum, medulla, pons, and peduncles presented a normal appearance. All the cranial nerves could be identified, and the blood-vessels were normal as far as could be determined. The left optic thalamus was relatively small; the left optic tract can be followed round to a shrunken geniculate body. The right optic thalamus much smaller and shrunken. On section it was honeycombed. The left optic tract and geniculate body very small. Optic chiasma well developed.

A transverse section through the right cerebral lobe at the level of the corpus callosum showed that the lateral ventricle was, if anything, slightly dilated, and that the ependyma and choroid plexus were normal. The brain substance beneath the ependyma had a spongy reticulated appearance, and in the floor of the ventricle beneath its lining membrane was a small cavity about the size of a pea, into which a haemorrhage had taken place. The left ventricle was almost normal in size, and the appearances closely corresponded to those of the right side, except that posteriorly the descending horn of the lateral ventricle was bounded by the haemorrhage previously referred to. The cortex of the mesial aspect of the cerebrum, when cut into, showed numerous small spaces about the size of a hemp seed. The foramen of Monro was patent and normal. The third and fourth ventricles were not enlarged, and the patency of the iter was established.

#### REFERENCE.

1. Trevor and Rolleston, *Proc. Roy. Soc. Med. Lond.* (Sect. for Study of Disease in Children), 1911-12, v. 1. 49.

## LIST OF ILLUSTRATIONS.

PLATE 3, FIG. I. (Case 1.) Typical attitude during life, showing head retraction, opisthotonos, and pleurosthotonos, with flexion of the arms and extension of the legs.

FIG. II. (Case 2.) Same as I. Note the similarity of the attitude in the two cases.

PLATE 4, FIGS. III and IV. (Case 2.) Polygraph tracings of the respiratory movements, showing the irregular character of the breathing, the periods of apnoea and of tachypnoea (rate of 160 respirations per minute).

PLATE 5, FIG. V. (Case 2.) Polygraph tracing of respiratory movements immediately before death. Note the gradual disappearance of the smaller respiratory curves, and the persistence of the large one to the end, in diminishing range and at increasing intervals. This tracing shows the movements accompanying death from respiratory failure.

FIG. VI. (Case 1.) The skull-cap has been removed, and the brain, covered with pia arachnoid, is seen lying on the base of the skull. Note the amount of shrinking of the cerebrum as indicated by the space around, which was filled with fluid.

PLATE 6, FIG. VII. (Case 2.) The brain viewed from above after removal of the pia arachnoid. Extensive recent haemorrhage into the posterior part of the left occipital lobe.

FIG. VIII. (Case 2.) The brain viewed from the right side. Cerebrum very shrunken and cerebellum normal.

PLATE 7, FIG. IX. (Case 2.) The brain from above. The lateral ventricles have been opened and the cerebellum and pons divided mesially. Section made through blood-clot in posterior part of the left occipital lobe.

FIG. X. (Case 2.) Micro-photograph of shrunken cerebrum, showing the homogeneous structure and the reticulated appearance.







FIG. 1

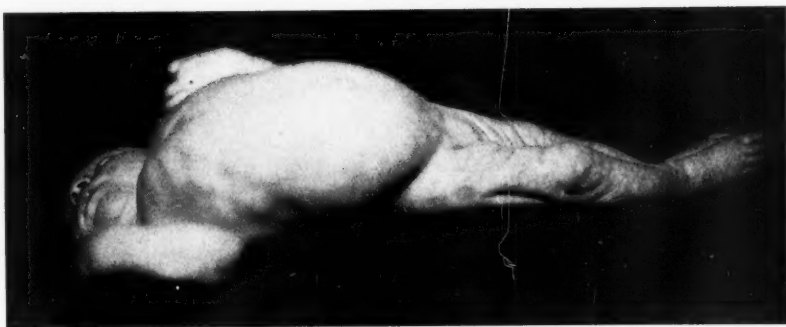


FIG. 2



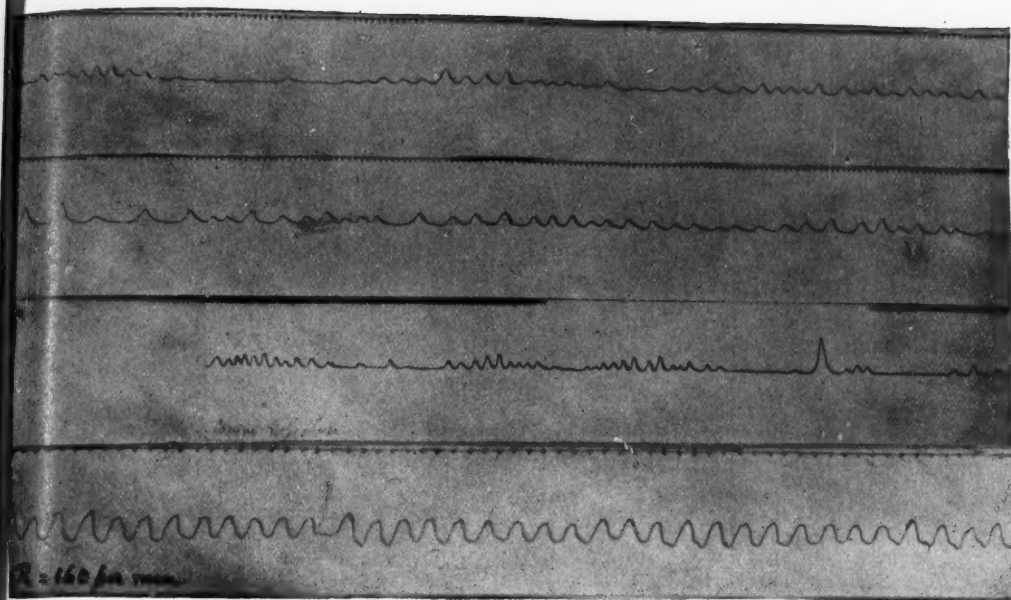


FIG. 3

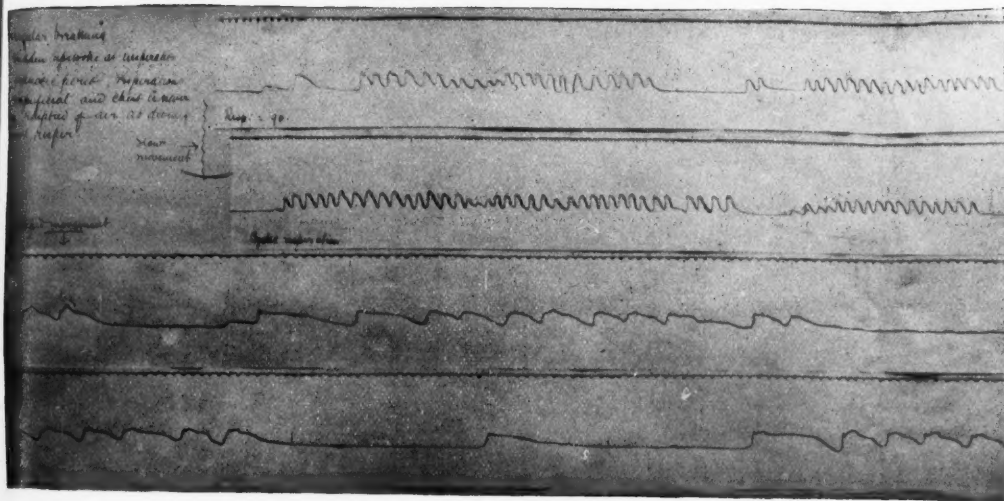


FIG. 4



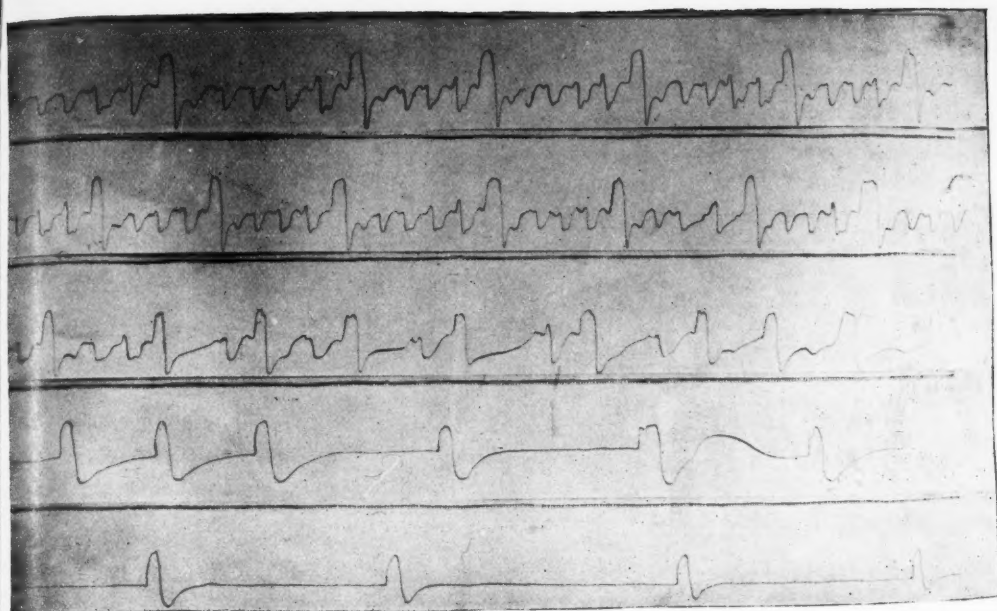


FIG. 5



FIG. 6







FIG. 7

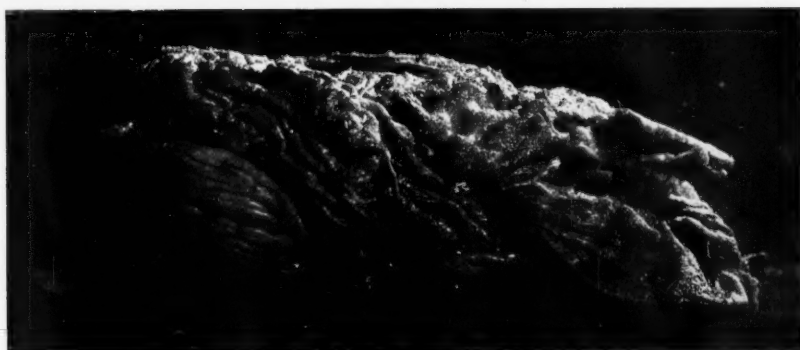


FIG. 8





FIG. 9

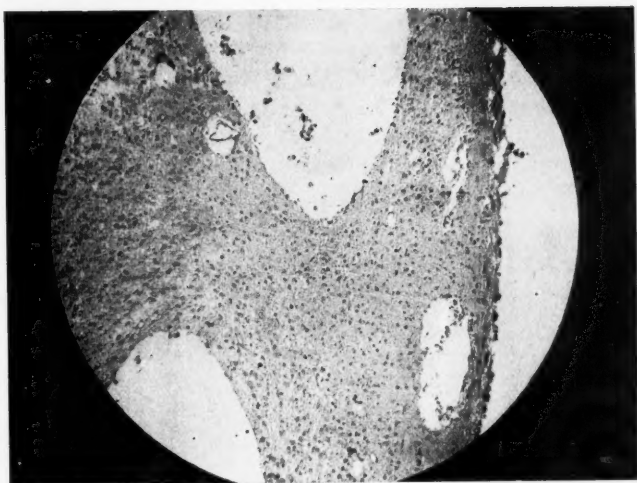


FIG. 10



## ON SULPHAEMOGLOBINAEMIA

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THE comparative rarity of the condition known as sulphaemoglobinaemia would appear in itself a sufficient justification for placing on record an account of new cases. Although this is one of the objects of this paper, certain observations made during an investigation of one of the cases have brought to light some new features, which seem to warrant an extended report. In all, the writer has had the opportunity of examining five authentic cases of this disease, and of carrying out an investigation along somewhat new lines of attack. The results are embodied in the present communication with the hope that the disease will receive general recognition, and also be the means of bringing to light the existence of other cases. The chief clinical feature of this disease is the marked cyanosis, with the absence of any physical signs in the chest to suggest disease of the heart and lungs. The patients show a leaden-blue colour of the lips, tongue, and nails, but no evidence of dyspnoea, and the blood-count is usually normal. The cyanosis is due to an alteration in the chemical constitution of the normal blood pigment haemoglobin. An entirely new and definite compound, known as sulphaemoglobin, partially takes the place of the oxy-haemoglobin, the blood changing from a bright red to a chocolate-brown colour. Seeing that the condition is due to this pigment in the blood, and further that it gives a characteristic spectrum, it follows that there is only one method of diagnosis, and that is by means of a spectroscopic examination of the patient's blood. Examination of the ear by trans-illumination is often quite sufficient to reveal the presence of this compound and the cause of the cyanosis. The value of such an examination cannot be too strongly emphasized, as the prognosis is favourable compared with those cases where the cyanosis is due to other causes. In the opinion of the writer this disease is much more common than one would suppose, and in discussing the subject with medical men of wide experience they invariably state that they have seen cases of this nature.

### *The Chemical Characters of Sulphaemoglobin.*

As sulphaemoglobin is responsible for all the colour-changes of the disease, a brief account of this pigment and allied blood pigments may not be out of place

[Q. J. M., Oct., 1913.]

here. The action of sulphuretted hydrogen on blood was first observed by Hoppe-Seyler (1), and the green compound formed was called by Araki sulphomethaemoglobin. Hoppe-Seyler further stated that this substance could not be obtained from reduced haemoglobin, but this result has not been accepted by recent workers upon the subject. Harnack (2), however, succeeded in preparing sulphaemoglobin by the use of reduced haemoglobin while he was investigating the action of sulphuretted hydrogen upon haemoglobin. If such a solution be examined spectroscopically, in addition to the broad band of reduced haemoglobin in the green, an additional band appears in the orange red between the Fraunhofer lines C and D, but nearer to the C line. This band, when measured, extends from  $\lambda$  610 to  $\lambda$  625. The band closely corresponds to that of methaemoglobin, but is slightly nearer to the yellow end of the red. Although these two derivatives of haemoglobin show similar spectra they can be easily distinguished by chemical tests. The addition of ammonia or ammonium sulphide to the blood causes the band of methaemoglobin to disappear, whereas that of sulphaemoglobin remains unaffected by such treatment. Wood Clarke and Hurtley (3) discovered another test which serves to distinguish these two pigments. If acid-free carbon monoxide be passed through the solution of sulphaemoglobin, all the bands are shifted towards the blue end of the spectrum, the band in the red changing from  $\lambda$  610-25 to  $\lambda$  605-20. This compound with its characteristic spectrum was designated by them carboxysulphaemoglobin. Solutions of methaemoglobin similarly treated showed no change. These tests are very important from the point of view of diagnosis, as it often becomes necessary to exclude methaemoglobin as a cause of the cyanosis. The brown pigment methaemoglobin occurs in the blood after the use of certain drugs, especially nitrites, potassium chlorate, and the coal-tar derivatives, e.g. acetanilide, phenacetin, sulphonol, and trional. In all cases of cyanosis, therefore, indulgence in such drugs must be excluded.

Wood Clarke and Hurtley, as the result of an investigation of the pigment sulphaemoglobin, came to the conclusion that it existed as an individual substance, but only in aqueous solution; and that it was a definite haemoglobin derivative. They also showed that powerful reducing agents greatly accelerate the production of sulphaemoglobin from oxyhaemoglobin treated with minute traces of sulphuretted hydrogen. These observations were of great value, since they form the basis of all the work described in this paper. The same view has since been advocated by Garrod in his article on 'Enterogenous Cyanosis' in Allbutt and Rolleston's *System of Medicine*. This hypothesis formed the starting-point of my work, and it is very gratifying to be able to establish it upon an experimental basis, particularly as the work has all been carried out in this hospital.



*Historical.*

Since the recognition of the disease depends entirely upon a spectroscopic examination of the blood it follows that our knowledge of this condition is of comparatively recent date. If one may be allowed to speculate, it seems highly probable that the following description, taken from Macaulay's *History of England*, vol. XI, chap. xv, p. 145, refers to a case of this nature: 'Carmarthen . . . had pleaded ill health . . . and the plea was not without foundation, for his digestive organs had some morbid peculiarities which puzzled the whole College of Physicians: his complexion was livid, his frame was meagre, and his face, handsome and intellectual as it was, had a haggard look which indicated the restlessness of pain as well as the restlessness of ambition.' This account is of great interest as it conveys a very good idea of the clinical picture of such cases of cyanosis.

Turning now to more recent times, it is of interest to note that practically all our knowledge of this particular form of cyanosis has been obtained by Dutch and English writers. Stokvis (4) was the first to describe a case of 'autotoxic enterogenous cyanosis' occurring in a soldier. The patient had suffered from cyanosis for five years, and this was associated with chronic diarrhoea. Spectroscopic examination of the blood showed the presence of large quantities of methaemoglobin. The urine of this patient contained nitrites, and gave with hydrochloric acid a red colour. There was also an excess of ethereal sulphates. Stokvis came to the conclusion that the cyanosis in his patient was due to a toxin derived from intestinal putrefaction, and this was the body giving the red coloration with acids.

Talma (5) described three similar cases, and further proved that the methaemoglobin was intra-corpuseular.

Since drugs were excluded in all the above cases, and having in view the fact that, at the time of writing, sulphaemoglobin was not known to Stokvis and Talma, it is quite possible that these cases represented examples of sulphaemoglobinaemia. Hijmans van der Bergh (6), working on sulphaemoglobin, added much valuable knowledge to the subject, describing in all four cases. The first case occurred in a boy, nine years of age, who was suffering from a rectal stricture, with a recto-vesical fistula. After operation, which provided a means of complete evacuation of the bowels, the patient recovered. The other cases all showed marked constipation and the cyanosis improved under treatment.

Van der Bergh (6) demonstrated that organisms which produced sulphuretted hydrogen when isolated from the stools were capable of transforming haemoglobin into sulphaemoglobin, and, further, the stools of the patient were particularly capable of bringing about this transformation *in vitro*. To van der Bergh we owe the recognition of sulphaemoglobinaemia as a distinct disease, and by the use of the ammonium sulphide test its distinction from methaemoglobin in the blood. With regard to methaemoglobin he showed that it was constantly associated with chronic diarrhoea, and that the cyanosis disappeared in these

cases when a strict milk diet was employed. The presence of nitrites in the urine and the red coloration produced with acids, as observed by Stokvis, was regarded by van der Bergh as a result of putrefactive changes. In the cases, however, of methaemoglobinaemia he, in conjunction with Grutterink (7), demonstrated that nitrites occur in the blood.

Gibson and Douglas (8) recorded a case of methaemoglobinaemia which presented some interesting features. The patient was a woman, aged 36, who had suffered from cyanosis associated with weakness, headache, and diarrhoea for three years. She gave a history of the use of drugs of the coal-tar group, which might have explained the occurrence of methaemoglobin in her blood. The blood on examination showed the spectroscopic characters of methaemoglobin, and also the presence of nitrites. The blood-count gave figures of 3,360,000 for the red cells, and 10,000 white cells. An interesting feature was the suggestive occurrence of *Bacillus coli communis* in the blood, although the observations were not definitely conclusive. On account of this finding they designated their case one of *microbic cyanosis*.

The contribution of West and Wood Clarke (9) added much valuable knowledge to the subject of sulphaemoglobinaemia, the work having been carried out upon a case under the care of Dr. Samuel West in St. Bartholomew's Hospital. The subject was a woman, aged 37 years, who had suffered for some years from cyanosis, weakness, and constipation. Physical examination of the chest did not reveal any signs of disease, and there was no dyspnoea. The blood examinations were normal as regards the red and white blood corpuscles. The use of drugs was excluded both by careful inquiries and direct observations, consequently the cyanosis could not be accounted for in this way. The examination of the spectroscopic characters of the blood was of interest, since in the first place methaemoglobin was detected. Chemical investigation of the blood, however, by Wood Clarke revealed the presence of sulphaemoglobin. It was shown by the position of the bands ranging from  $\lambda$  613 to  $\lambda$  629 in one instance, and from  $\lambda$  612 to  $\lambda$  628 in another, and this conclusion was confirmed by the application of the ammonium sulphide and carbon monoxide tests. An attempt was made to demonstrate the presence of minute quantities of sulphuretted hydrogen in the blood, but in spite of the fact that a very delicate test was used the results proved negative. Observations, however, upon the amount of sulphuretted hydrogen required to produce sulphaemoglobin in blood showed that only extremely minute quantities of this gas were necessary, and so the negative findings did not appear surprising. The presence of organisms in the blood was not revealed by growth upon various media. The urinary analysis showed only traces of nitrites in acid urine and a subnormal amount of ethereal sulphates, and did not give any evidence of abnormal pigments or diamines. The stools were also analysed for the presence of an abnormal amount of sulphuretted hydrogen, and for an abnormal content of  $H_2S$ -forming organisms, but the results proved to be negative upon both points. The conclusion, therefore, was arrived at, that the patient was suffering from

idiopathic sulphaemoglobinaemia (enterogenous cyanosis), but the exact cause of the condition was not ascertained.

These observations of West and Wood Clarke represented a very careful and laborious attempt to elucidate the problem, and great credit is due to them for having paved the way for future work upon the subject. Their paper included a summary of the literature upon the subject up to the time of writing.

Russell (10) in 1907 described another case which at first was diagnosed as methaemoglobinaemia, but later proved to be one of sulphaemoglobinaemia. The patient was a woman, aged 31, suffering from prolonged anaemia of the chlorotic type. There was also bone disease, and recurrent bruising and ecchymosis of the right arm, and, in addition, she presented the typical signs and symptoms of sulphaemoglobinaemia, viz. cyanosis, weakness, headache, and habitual constipation. An interesting feature of the case was the occurrence of paroxysmal attacks of dyspnoea, which were apparently functional. Examination of the heart revealed no abnormalities apart from some slight enlargement of the right side when examined on the X-ray screen. The cyanosis showed the characteristic variations in intensity, and with free purgation almost disappeared. On two occasions blood-counts were made and appeared practically normal. Examination of the blood, when carried out under the directions given in the paper by West and Wood Clarke, showed the presence of sulphaemoglobin.

Essex Wynter (11) showed a case of cyanosis at the meeting of the Clinical Section of the Royal Society of Medicine. The patient was a woman, aged 45 years, who had been under his observation since 1902, having suffered from anaemia and cyanosis for two years. She had a yellowish pallor, marked cyanosis, weakness, constipation, anorexia, and occasional vomiting. The blood was of a chocolate colour, and did not undergo any change with the passage of carbon monoxide gas. Spectroscopically, it showed a band in the red which disappeared on the addition of ammonium sulphide. A blood-count showed 3,000,000 red cells and 7,000 white cells. The haemoglobin amounted to 50 per cent, and the colour index was 0.74. A blood-culture was made, but no growth occurred. The case when shown was found to present so many points of interest that a committee was appointed to make further investigations. In their report they state that in 1895 the patient was suffering from cyanosis and anaemia of two years' duration. The blood-count at this time was 4,000,000 red cells, and the haemoglobin 50 per cent. In 1896 the blood-count fell to 2,500,000. The patient later had continuous slight pyrexia, with occasional bursts of high temperature, some of which followed the administration of suprarenal extract. Examination of the blood showed the red cells to be well formed, and the absence of nucleated red-blood corpuscles. The serum was not abnormally coloured. Spectroscopically, the blood showed a narrow band in the red ranging from  $\lambda$  610 to  $\lambda$  625, which was not removed by the addition of ammonium sulphide, and gave the characteristic spectral changes after the

passage of carbon monoxide, namely, the shifting of the band towards the D line. The urine had a brownish tint, and did not contain nitrites. The committee reported, therefore, that the case was one of sulphaemoglobinaemia.

Wood Clarke and Curtis (13) in 1910 gave an account of the first recorded case of sulphaemoglobinaemia in America. Their patient was a woman, aged 24, with cyanosis, weakness, and constipation. There were no physical signs to be found in the chest or elsewhere. The blood when withdrawn was a rich chocolate colour, and was found to contain sulphaemoglobin. The blood-count was normal, and a blood-culture proved sterile. The stools did not show any abnormal features, and no evidence of intestinal putrefaction could be obtained from the urinary analysis. The cyanosis in this case was clearly due to sulphaemoglobinaemia, and showed the same intermittent nature of the attacks.

More recently, Haldin Davis (14) has described a case of intra-corpuseular sulphaemoglobinaemia in a woman, aged 27, who was suffering from cyanosis with weakness, fainting attacks, headache, and constipation. An examination of the blood revealed the presence of a band in the red of the spectrum which appeared to resemble that of sulphaemoglobin. Physical examination of the chest showed nothing abnormal, and a blood-count also proved normal. This case will be again referred to later in this paper.

The above account represents a brief summary of the literature, and includes the recorded cases of cyanosis due to sulphaemoglobinaemia and methaemoglobinaemia. The earlier cases are surrounded with some degree of uncertainty since the two conditions were not then recognized. If, therefore, we exclude the case of Stokvis and the three cases of Talma, we find nine authentic cases of sulphaemoglobinaemia recorded. In these nine cases all were females, with the exception of van der Bergh's boy with a urethro-rectal fistula. In all the patients no definite physical signs were found in the chest, and no evidence of any pathological lesion was obtained. The symptoms presented by all were similar, namely, cyanosis, weakness, headache, and constipation. In all cases where a blood-count was done the figures appeared practically normal, and blood-cultures were all sterile. In methaemoglobinaemia, on the other hand, three out of the four cases occurred in males, and these were all adults. The most marked symptom was the constant occurrence of diarrhoea, and this seems in itself to provide a distinction between the two conditions apart from the changes in the blood. Nitrites were found in the blood in three cases. Under treatment the four sulphaemoglobinaemia patients of van der Bergh recovered when the constipation was treated. The other recorded cases have remained apparently *in statu quo*. With methaemoglobinaemia, on the other hand, temporary improvement followed upon the adoption of a milk diet.

The cases of sulphaemoglobinaemia described by West and Wood Clarke and by Essex Wynter I have had the opportunity of investigating further, and three new cases will also be described.

*Dr. Garrod's Case. No. 1.* E. B., a nurse, aged 27 years, was admitted to St. Bartholomew's Hospital under the care of Dr. Garrod on February 14, 1912. Previous to this date the patient had on two occasions been treated as an in-patient at the Great Northern Hospital under Dr. T. J. Horder, who subsequently sent the case to Dr. Garrod for further investigation. The illness began about three years ago with attacks of faintness and dizziness, which increased with exertion. During these attacks she became quite blue, but assumed an almost normal appearance during the intervals. The history of the present illness shows a series of similar attacks, associated with a slaty-blue coloration of the skin and mucous membranes, followed by intervals of varying duration, when the normal appearance of the body returned. During her stay in the Great Northern Hospital nothing abnormal was noted in the heart and lungs, and an examination of the blood revealed no definite evidence of the condition. Her blood-count averaged:

Red blood corpuscles . . . . .	4,000,000 to 5,000,000.
White blood corpuscles . . . . .	8,000 to 12,000.
Haemoglobin . . . . .	80 per cent.

A blood-culture proved to be sterile.

The von Pirquet reaction was negative, and skiagraphy gave no help.

*Past history.* Rheumatism at the ages of 12 and 21. Her joints were swollen, but there is no record of any affection of her heart. She had scarlet fever when a child. The catamenia have been normal as regards frequency, quantity, duration, and absence of pain. She is not usually constipated and micturition has been natural, but during the last fortnight the amount of urine passed has been diminished.

*Family history.* Nothing of importance. Parents both living, but 'rheumatic'.

*Condition on admission.* An unhealthy-looking girl with a muddy complexion and lips markedly cyanosed. Eyes natural. Tongue furred, dry, and blue. Fauces natural. Teeth fair. Neck—no enlarged glands felt. Chest, lungs, and heart natural. Abdomen—liver dullness extends from the seventh rib above to the costal margin below. The spleen is not to be felt. Lower limbs—knee-jerks obtained. Urine dark in colour. Stools loose but normal in appearance. The fingers were not clubbed. von Pirquet positive, but more marked with human than with bovine tuberculin.

On admission to St. Bartholomew's Hospital her condition was diagnosed by Dr. Garrod, and subsequent examination of the blood spectroscopically showed a band in the red region between  $\lambda$  613 and  $\lambda$  625, corresponding to that of sulphaemoglobin. This was confirmed by the application of the ammonium sulphide test described by van der Bergh of Rotterdam.

On February 16 a blood-culture was made and proved to be sterile. The stools were also examined and Gram-negative organisms found to preponderate. Cultures were made, and all the organisms tested gave the reactions of *B. coli communis*. No blood or mucus was found.

On March 7 samples of blood were obtained with the object of detecting a reducing substance. The procedure consisted in adding various quantities of the patient's blood to a dilute solution of normal blood, and observing any changes which took place by means of the spectroscope. It was found that a few drops of the sulphaemoglobin blood would reduce a solution of oxyhaemoglobin, the two bands of the latter being quickly replaced by the single band of the former.

This experiment, though simple, was very striking, and clearly demonstrated that a powerful reducing agent was present in the sulphaemoglobin blood.



A subsequent search for a reducing substance in the various secretions and excretions revealed the presence of nitrites in larger quantity in freshly passed urine and also in the saliva. At this stage of the work I consulted Dr. Gordon as to the possibility of a microbial infection yielding nitrites as a by-product, and with his valuable help steps were taken to isolate such a nitrite-producing organism. The results will be given in detail later.

March 9. A twenty-four-hour specimen of the urine was obtained and a complete analysis carried out. The ethereal sulphates were found not to be increased, but were rather subnormal in amount, and indican was present in small quantity. On this date and subsequently nitrites were detected in the urine.

March 11. The saliva contained abundant nitrites as judged by the Greiss-Ilosvay reagent, and similarly the urine.

March 12. Oxygen was administered to the patient by means of a nitrous oxide inhaler, with the result of a transitory reduction in the cyanosis after ten minutes' inhalation. The disappearance of the blue colour was associated with the absence of nitrites from the urine and saliva. On subsequent days the same treatment was adopted with like results.

On March 14 the blood-pressure was equivalent to 122 mm. mercury. The blue colour of the patient from this time to the end of her stay in the hospital showed marked variations in intensity. In all there were four distinct attacks of cyanosis, which in one instance came on suddenly, and as rapidly disappeared. During the intervals of freedom from attack, the colour of the face and mucous membranes resembled that of a normal person. An attack was generally preceded by headache, which persisted and became very severe, and sleeplessness was also complained of. The band of sulphaemoglobin could at these times be easily detected by examination of the ear with a hand spectroscope, and abundant nitrites were usually found in the saliva. The patient was given intestinal antiseptics, particularly liquid paraffin, without any appreciable diminution in the blue colour. Administration of oxygen by means of a nitrous oxide inhaler invariably produced a transitory diminution in the blueness. Daily baths at a temperature of 105–110° F. were given, but without any appreciable effect.

On May 6 a course of vaccine treatment was adopted, the nitrite-producing organism isolated from the patient's saliva being used. Three doses of 10, 25, and 50 millions were administered on alternate days, but did not produce any appreciable effect. The second attack supervened during the course of vaccine treatment. On July 1 a further course was given, proceeding from 10 millions up to 100 millions, which produced no definite effect, although the cyanosis varied from day to day and the general condition of the patient showed slight improvement. Three bad teeth and a stump were later removed, and doses of 100, 250, and 500 millions of the vaccine given.

The patient then left the hospital much improved, but attended for a few weeks in order to receive further doses of 500 millions of the vaccine. At the end of October, 1912, the blue colour had entirely disappeared from the lips and mucous membranes and the patient presented a perfectly normal appearance.

Since that date she has remained quite well, and has been able to resume her occupation as a nurse. Repeated examination of the blood has failed to detect any sulphaemoglobin, and the nitrite-forming organism has not been isolated from the saliva. This latter result is all the more striking since during the earlier stages of the disease the organism was present in large numbers.

*Dr. Garrod's Case. No. 2.* G. P., a female, aged 28, was admitted to St. Bartholomew's Hospital, under the care of Dr. A. E. Garrod, suffering from cyanosis, which was mainly confined to the facial area. The blueness was first



noticed twelve years before, and she has never been free from blueness since, although it has varied in intensity. At the end of April, 1912, on the advice of Dr. Haldin Davis, she attended St. Bartholomew's Hospital, and was admitted. A description of the case has already been published by Dr. Haldin Davis (14), and this paper is referred to in the summary of the literature given above.

The patient complained of weakness, fainting attacks, headache, and constipation. On examination no definite physical signs were found in the chest, and no pathological lesion elsewhere in the body could be discovered. During her stay in hospital the blueness appeared universal, but varied in intensity from day to day. The blood-count showed the following features:

Red blood corpuscles	. . . . .	5,000,000
Haemoglobin	. . . . .	102 per cent.
Colour index	. . . . .	1.02
White blood corpuscles	. . . . .	10,800

A differential count showed:

Polymorphonuclears	. . . . .	6,800 per c.mm.	73.5 per cent.
Lymphocytes	. . . . .	1,570 " "	17.0 " "
Large mononuclears	. . . . .	456 " "	4.9 " "
Eosinophils	. . . . .	370 " "	4.0 " "
Basophils	. . . . .	56 " "	0.6 " "

No abnormal cells were found.

The blood when examined spectroscopically showed a distinct band in the red region, and since this did not disappear on the addition of ammonium sulphide, it was presumably sulphaemoglobin. The saliva yielded a well-marked reaction for nitrites, and a pure culture of a nitrite-forming organism was isolated. The urine appeared normal both in colour and general chemical characters, and no nitrites were found in specimens freshly voided.

Further investigations were in progress finally to settle the diagnosis, when the patient discharged herself, having apparently lost patience after so many years spent in the wards of various hospitals.

*Case No. 3.* F. S., female, aged 37, married, has been under the care of Dr. Ernest Ringrose, of Newark, since January, 1909, suffering from cyanosis.

*Past history.* When 15 years old patient had severe anaemia, and was in Grimsby Hospital. Fourteen years ago she had acute rheumatism. At this time she also had refraction trouble, for which glasses were prescribed. Her teeth were all removed under ether also at this period. Six years before the patient gave up wearing glasses and has suffered from bad headaches ever since, for which she has taken phenacetin, and the cyanosis also dates from the last five years. She has had six children, all easy confinements. Three of the children are living, two died of phthisis and one of diphtheria.

*Family history.* Her father died of bronchitis twenty years before, and her mother is still alive and healthy. One brother died of phthisis, and one is alive and healthy. Two sisters, one healthy and one very anaemic.

*Condition on admission.* A big well-developed woman. Her skin presents a pale-blue colour, with blue lips and nails. The whole appearance of the patient is similar to that observed by a person standing under a mercury vapour lamp. There are no signs of oedema.

Eyes—Optic disks normal, veins engorged. Marked astigmatism.

Respiratory system—Slight dyspnoea, which becomes very marked on exertion. Lungs normal.

Circulatory system—A loud systolic murmur heard at the apex. Pulse 80, regular low tension. On pricking the ear the blood is very dark in colour and rapidly clots. Haemoglobin, 55 per cent. Leucocytes, 7·600 per c.mm. Colour index, 0·89.

Abdomen—Spleen felt one finger's breadth below the costal margin. Otherwise nothing abnormal found.

Nervous system—No objective signs of disease; sleeplessness and severe headaches.

Urine—No frequency. Clear, sp. gr. 1020. Acid. No albumin or sugar.

Treatment—The patient has been treated with salines and intestinal antiseptics without any appreciable diminution of the colour. Vaccine treatment.

When seen in October, 1912, the patient presented well-marked cyanosis. Examination of the blood showed a well-marked band in the red end of the spectrum, which proved to be that of sulphaemoglobin. The serum gave the reduction test as previously described. The saliva contained nitrites, and on cultivation yielded a nitrite-forming organism which was isolated in pure culture. From this an autogenous vaccine was prepared, which was kindly administered by Dr. Ringrose. He reported that the course of vaccine treatment ranging from 10 up to 250 millions did not produce any diminution of the blue colour of the patient.

#### *Chemical Investigations of Case I.*

*The blood.* On February 15 a sample of blood was withdrawn from the ear of the patient and examined spectroscopically. A well-marked band in the red region of the spectrum was seen similar to that of sulphaemoglobin. On treatment with ammonium sulphide the band did not disappear.

On February 16 blood was taken for blood-culture, and at the same time for chemical investigation. No growth took place on incubation at 37° C., nor at room temperature. The blood was submitted to spectroscopic examination and a band in the red detected between the  $\lambda$  613 and  $\lambda$  625. That this band was the characteristic band of sulphaemoglobin was definitely proved by submitting the blood to the ammonium sulphide test, and to the carbon monoxide test of Wood Clarke and Hurlley as previously described.

The serum was separated from a sample of the blood and found to be quite clear and of normal colour.

Attempts were made to ascertain the presence of a reducing substance in the patient's blood serum, and the following procedure was adopted. A dilute solution of normal human blood was placed in several flat-sided cells, and to these were added varying quantities of the patient's serum, ranging from

0.1 c.c. up to 2 c.c. The solutions were mixed carefully by means of a platinum needle, and examined spectroscopically. The oxyhaemoglobin bands were found to be rapidly replaced by the broad band of reduced haemoglobin, and the corresponding colour changes could be seen with the naked eye. The results were controlled with normal human blood and mixtures of serum and blood from normal individuals. These results led to the supposition that a reducing substance was present in the blood. Careful analysis of the serum revealed the presence of nitrites, but it seemed highly probable from controls made with potassium nitrite and blood that a much more potent reducing agent was present in the serum. Repeated attempts were made to detect other reducing substances, but without success. This may possibly be accounted for by the difficulties encountered in dealing with only small amounts of blood.

On two occasions the haemoglobin in the blood was estimated by Dr. Fowell, and also the total iron content of the blood.

The following figures were obtained:

Total Iron.	Haemoglobin.	Non-haemoglobin Iron.
0.040	80	0.007
0.041	84	0.007

*The saliva.* The saliva of the patient was collected directly into sterile tubes and at once sealed. On arrival at the laboratory the various samples were tested immediately with the Greiss-Ilosvay reagent for nitrites. An intense red coloration which developed at once was regarded as a positive test for the presence of nitrites. The same sample was also treated with metaphenylenediamine and sulphuric acid, a blue coloration indicating nitrites. The effects of various forms of treatment were followed by observations upon the saliva, and in some instances the amount of nitrite present was estimated. Attempts were at first made to make quantitative determinations by a colorimetric method using Magenta S. as a standard. This method, however, did not give very satisfactory results, and the method of destruction of nitrites by hydrazine sulphate was substituted. It was found that the nitrites in the saliva varied from 0.018 to 0.05 gm. per cent. calculated as potassium nitrite. In every case control observations were made with saliva from normal individuals, but only minute quantities of nitrites were obtained. The presence of sulphocyanides was also observed in the saliva, but no abnormal amount could be detected. The results of the examination of the saliva will be best given in tabular form.

Date.	Time.	Nitrites.	Sulphocyanides.	Treatment and Appearance.
March 7, 1912	10.30 a.m.	+	0	Nil. Patient very blue.
" 12, "	10.55 a.m.	0	0	Oxygen administered at 9.30 a.m.; ten minutes' administration.
" " "	3 p.m.	+	0	
" " "	7.30 p.m.	++	0	
" 13, "	1 a.m.	+	0	
" " "	5.45 a.m.	+	0	Patient very blue. Blood pressure 122 mm. Hg.
" 18, "	11.50 a.m.	+	0	
" " "	7 p.m.	0	0	
" 19, "	3.30 p.m.	+	0	
" " "	7.50 p.m.	+	0	
April 14, "	11 a.m.	0	0	
" " "	8 p.m.	0	0	
" 15, "	9.30 a.m.	++	0	
" " "	7.30 p.m.	0	0	Blueness returning after being absent for 10 days.
" 16, "	10.45 a.m.	faintly +	0	
" " "	6.30 p.m.	+	0	
" 17, "	10.30 a.m.	+	0	
" " "	7.45 a.m.	+	0	
" 18, "	7 p.m.	0	0	
" 21, "	7 p.m.	0	0	
" 22, "	10.30 a.m.	+	0	On 25th very deep blue colour.
May 13, "	11 a.m.	+	0	Blueness increased.
" " "	3 p.m.	0	0	
" " "	7 p.m.	++	+	
" 14, "	7.30 p.m.	0	+	
" 15, "	11 a.m.	0	0	
" 16, "	6.30 p.m.	0	0	
" 17, "	10 a.m.	0	0	
" 18, "	11 a.m.	0	0	Blueness still very marked.
" " "	5 p.m.	0	0	
" " "	8 p.m.	0	0	
" 19, "	11 a.m.	0	0	
" " "	8 p.m.	0	0	
" " "	7 p.m.	0	0	
" 20, "	10.30 a.m.	0	0	Oxygen given for ten minutes.
" 23, "	7 p.m.	0	0	Very blue. Hot baths begun.

On and after this date the saliva when tested showed only minute quantities of nitrite similar to that found in many normal individuals. The results given in the table do not demonstrate any indication of a relationship between the blueness and the occurrence of nitrites in the saliva, although, speaking generally, the absence of blueness corresponded with a disappearance or diminution of the nitrite reaction. The remainder of the work upon the saliva was directed to the isolation and cultivation of the organism which was probably responsible for the excess of nitrites present. A description of the work will be found in a later part of this communication.

*The urine.* The analysis of the urine was considerably complicated during the earlier part of the work by the small amounts passed in the twenty-four hours. The urine was dark in colour and highly concentrated. A noticeable feature of these specimens was the intense blackening of the urine on standing, the nature of the change being quite inexplicable. All the specimens gave intense nitrite reactions when freshly voided. The patient was later placed upon a known weighed diet and a complete urinary analysis made. The following figures were obtained upon a twenty-four-hour specimen :

Volume . . . . .	750 c.c.	
Reaction . . . . .	acid	
Sp. gr. . . . .	1022	
Indican . . . . .	traces	
Sugar . . . . .	absent	
Albumin . . . . .	absent	
Total acidity . . . . .	52.4 % $\frac{N}{10}$ NaOH	= 393 total.
Total nitrogen . . . . .	1.5 %	= 11.25 gr. total.
Creatinine . . . . .	0.112 %	= 0.84 " "
Creatine . . . . .	0.00 %	= 0.00 " "
Total sulphur as SO <sub>3</sub> . . . . .	2.59 %	
Inorganic sulphur as SO <sub>3</sub> . . . . .	2.22 %	
Ethereal sulphur (SO <sub>3</sub> ) . . . . .	0.10 %	
Neutral sulphur (SO <sub>3</sub> ) . . . . .	0.27 %	

These results do not give any indication of intestinal putrefaction and agreed quite closely with the observations of other writers upon sulphaemoglobinaemia.

*Stools.* A specimen of the stools was obtained and presented the following characters :

Appearance—A greenish-brown semi-solid stool.

Reaction—Alkaline.

Urobilin—Well-marked reaction.

Mucin—Present in small quantity.

Blood—Absent.

Nitrites—Absent.

Microscopically—Abundant triple phosphate crystals, a few muscle fibres and fat globules, and undigested vegetable debris.

Cultures of the stools were made with especial reference to a nitrite-forming bacillus, but no organism of this nature could be isolated from plate cultures.

*Case described by Drs. Samuel West and Wood Clarke.* Through the kindness of Dr. Steele, of Stoke Ferry, the writer was able to visit the patient in April, 1912, and found that the disease was still in progress. The saliva was obtained and inoculations made into broth at once. The saliva gave a well-marked reaction for nitrites, and also for sulphocyanides. Films prepared from the saliva showed many Gram-negative bacilli, and cultivation at 25° C. yielded the typical colonies of the nitroso-bacillus. Examination of the blood revealed the presence of the characteristic band in the red end of the spectrum, and also of a reducing substance in the serum. In every particular this patient therefore showed the same features as those found in the previous case.

*Case described by Dr. Essex Wynter.* At the kind invitation of Dr. Essex Wynter the writer saw the case he had described, and found the well-marked cyanosis still persisting. The blood was of a dark chocolate colour, and gave all the tests for sulphaemoglobin. The saliva contained abundant nitrites, and a pure culture of the nitroso-bacillus was isolated.

*The Isolation and Chemical Characters of the Nitroso-bacillus isolated from the Saliva.*

The presence of a reducing body in the blood of patients suffering from sulphaemoglobinaemia having been established, together with the constant occurrence of nitrites in the saliva, an attempt was made to ascertain, if possible, the origin of these substances. The blood of Case I had been cultivated on two occasions, and also the faeces, but from neither could any nitrite-forming bacillus be isolated. Since, however, the saliva contained appreciable quantities of nitrites, attention was particularly directed to this secretion, and also to the throat as a possible source of the chemical changes found.

The saliva of the patient was inoculated into tubes containing normal saliva, broth, gelatin, and milk, the media being first tested to exclude the presence of nitrites. The tubes were then incubated at 37° C., both aerobically and anaerobically, one series of tubes being inoculated with unheated saliva, whilst the other series was inoculated with saliva heated at 60° for one hour. In the unheated series a marked nitrite reaction occurred in the anaerobic gelatin culture only, and not in any of the other tubes; normal saliva cultivated under similar conditions gave negative results. The anaerobic gelatin culture containing nitrites showed microscopically mainly streptococci and Gram-positive bacilli. The saliva collected in sterile tubes at intervals during the day was again inoculated into gelatin, broth, and blood broth, heated and unheated saliva being used and grown both aerobically and anaerobically. Again nitrites were found only in the anaerobic gelatin tubes. Further, cultures grown aerobically at 20° C. showed no growth and no nitrite formation in twenty-four hours. On incubation at 37° C. for over twenty-four hours it was found that those tubes which had given a positive nitrite reaction now failed to do so, and further, the subcultures from these tubes did not contain any nitrite formers. These results therefore led to the conclusion that the nitroso-bacillus did not grow at 37° C., or if so, was rapidly destroyed at this temperature in *in vitro* experiments. The cultures in gelatin and broth were kept at room temperature for some weeks, and on repeated testing showed a strongly positive reaction with the Greiss-Ilosvay reagent for nitrites. Plate cultures were made upon gelatin and agar, and stored at room temperature, and a number of discrete colonies appeared. These were quite round, of a greyish translucent appearance, and produced abundant nitrites when subcultured into broth and gelatin media. Microscopical examination of films showed the presence of small short oval bacilli which were Gram negative and non-motile. Agglutination tests were applied to the serum of Case I, and subsequently to the sera of the other cases of sulphaemoglobinaemia, with negative results, but this was not surprising in view of the inherent tendency of the organisms to aggregate together apart from the action of any specific agglutinin. The chief feature observed in cultures of this organism was the very slow growth on ordinary media, and also the prolonged vitality under such conditions.



The relationship of temperature to the growth of this nitroso-bacillus proved of interest, since it had been determined quite early in the investigation that the organism would not grow at 37° C., and this was confirmed by subsequent cultivation in all forms of media. Cultures were therefore prepared in broth and on agar tubes and incubated at various temperatures for several hours, the agar tubes being used to indicate growth and the broth tubes for the detection of nitrite formation. The following results were obtained :

Temperature.	Agar.	Broth.
Room temperature 15° C.	Growth	Nitrites present
" 20° C.	Growth	"
" 25° C.	Abundant growth	Nitrites present in " quantity
" 30° C.	Growth	Nitrites present
" 35° C.	Growth	"
" 37° C.	No growth	No nitrites present

It would appear from this table that the organism attains its maximum development and metabolic activity at a temperature of 25° C., i.e. the optimum temperature, whereas a temperature of 37° C. completely inhibits its growth. The highest temperature of growth would therefore lie between 35° and 37° C.

*The Chemical Changes induced by the Nitroso-bacillus.*

The subcultures of the nitroso-bacillus were found to develop growth upon all forms of organic media, with the production of nitrites both at room temperature and also at 25° C.

In comparing its chemical reactions with those of allied organisms some very interesting results were obtained, as seen by examination of the following table :

Agar . . . . .	Growth.
Broth . . . . .	Growth and nitrite formation, but no indol.
Peptone broth . . .	Growth and abundant nitrites.
Milk . . . . .	Peptonization without acid formation, but nitrites produced.
Neutral red . . . .	Slowly reduced.
Glucose . . . . .	No acid and no gas, but nitrites formed.
Lactose . . . . .	No acid or gas.
Other sugars . . .	No change observed.
Broth, egg-white . .	Egg slightly digested, and medium becomes gelatinous.

From these reactions it will be seen that the organism is capable of utilizing organic media for its growth and metabolism, being able to disintegrate complex proteins. The slow liquefaction of gelatin, and also the absence of any chemical change in the sugar media, makes it difficult to place the bacillus in any one known group of organisms. Under the circumstances it became necessary to investigate the origin of the nitrites produced in organic media by the activity of this organism, as throughout media free from nitrites and also nitrates had been used. To determine this point a number of media were made containing organic nitrogenous compounds of different degrees of complexity, each com-

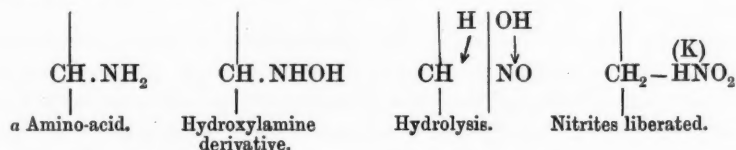
pound being dissolved in a mixture of salts known as Fischer's necessary salts. This mixture consisted of sodium chloride 5 grm., potassium phosphate 1 grm., magnesium sulphate 0.2 grm., calcium chloride 0.1 grm., and distilled water to 1 litre. All the chemicals used were chemically pure and free from nitrites, and as far as possible free from nitrates as well. The results may best be given in tabular form as follows, the tubes being incubated at room temperature and also 25° C., and control observations made in every case :

Medium.	Growth.	Nitrites.	Reducing substance.
Tap-water	Absent	Absent	Absent
Tap-water + necessary salts			
" " " " + Ammonium chloride	Slight	A trace only	"
" " " " + Potassium nitrate	"	Present	"
" " " " + Ammonium nitrate	"	"	"
" " " " + Ammonium sulphate	"	"	"
" " " " + Urea (pure)	Doubtful	Mere trace	"
" " " " + Urea containing trace of nitrates	Present	Present	"
" " " " + Urine	"	Trace	"
" " " " + Glycocoll	"	Merest trace	Trace
" " " " + Alanine	"	Present	Present
" " " " + Asparagine	"	Abundant	"
" " " " + Cystine	"	"	"
" " " " + Tyrosine	"	"	"
" " " " + Tryptophane	"	"	"
" " " " + Hippuric acid	"	Merest trace	Absent
" " " " + Glutaminic acid	Profuse growth	Very strong reaction	Present
" " " " + Histidine	Growth	Present	"

The above table demonstrates clearly the effect of the organism upon various nitrogenous substances of varying complexity. The most abundant growth occurred in the tubes containing asparagine, glutaminic acid, and tyrosine, and in these solutions the nitrite formation was also well marked, tending to show that the higher molecular amino-acids were destroyed more readily. The tyrosine and tryptophane solutions did not show any blackening, as one would expect if any oxydases were present. The cystine solutions were further examined in the hope that the production of sulphuretted hydrogen might be detected, and so provide a possible explanation of the production of the sulphæmoglobin in the blood of the patients infected with this organism. No sulphuretted hydrogen could be found in the cystine tubes or in broth tubes containing lead acetate, the sulphur being entirely recovered from the former, and presumably still in organic combination. It was thought that possibly the organism was capable of fixing nitrogen from the air, and to exclude this the following experiment was undertaken. A solution free from nitrates, consisting of the necessary salts, glucose, and water, was placed in a conical flask and one loopful of the organism inoculated. A growth was found, but nitrites were absent after incubation for several days both at room temperature and also at 25° C., indicating that the organism does not fix atmospheric nitrogen in the form of nitrites. In this particular the nitroso-bacillus would appear to be different from the other organisms of this class which have been described. At this juncture I would like to express my indebtedness to Dr. Bertrand of the

Pasteur Institute, who very kindly repeated many of these tests with identical results. In order to test the virulence of the organism in question Dr. Gordon kindly injected 500 millions into the ear vein of a rabbit weighing 2,560 grm. After twenty-four hours blood withdrawn from the ear showed no evidence of sulphaemoglobin and the rabbit remained unaffected by the injection. The nitroso-bacillus was evidently incapable of growing in the blood-stream and of producing sulphaemoglobin directly. The relation of this organism to sulphaemoglobinaemia is rendered even more striking, however, by the negative results obtained with the saliva of normal healthy individuals and those suffering from other diseases. A large number of specimens have been examined, and in no case was a similar organism isolated. In view of these control observations it would appear highly probable that this nitroso-bacillus had some definite relation to sulphaemoglobinaemia, but until more cases have been investigated no definite pronouncement can be made.

The results detailed above would, however, suggest that the saliva of the patient examined contained a nitrite-forming bacillus. This bacillus was also found in the saliva of all the other cases which I have had the opportunity of examining. This nitroso-bacillus has been isolated in pure culture, and when grown on the various media has given identically the same results. It would appear that the organism is capable of growing on all forms of organic media with the production of nitrites. Further growth occurred in media containing only necessary salts and an added amino-acid, the latter being disintegrated yielding amongst other substances nitrites in quantity. The simpler amino-acids and ammonium salts were only partially attacked, and the organism was apparently incapable of normal growth under such conditions. Perhaps the most striking results were obtained with cystine, as this sulphur-containing amino-acid was split up, but no trace of sulphuretted hydrogen was detected amongst the break-down products. In all cases where growth occurred with consequent utilization of the amino-acid a very strong reducing substance appeared in addition to the nitrites. On purely theoretical grounds it may be assumed that this reducing agent is of the nature of an hydroxylamine derivative, and the changes graphically represented in the following stages :



The hydroxylamine derivative may therefore be regarded as the reducing agent, and possibly the cause of the sulphaemoglobinaemia. The existence of such a nitroso-bacillus in the buccal cavity producing a reducing substance which is easily absorbed into the blood-stream would adequately account for the reduction of part of the oxyhaemoglobin and the presence of a reducing substance in the serum. The mere trace of sulphuretted hydrogen required to

produce sulphaemoglobinaemia under these conditions might easily be derived from the intestinal tract. This view receives corroboration from the fact that persons dying from sulphuretted hydrogen poisoning show no trace of the pigment sulphaemoglobin in their blood. Thus all the necessary factors for the production of sulphaemoglobinaemia are present, and this view would further provide an explanation of the special features of the disease in question, e.g. the periodicity and characteristic symptoms.

The disintegration of the amino-acid molecule with the liberation of nitrites resembles in some respects the action of such strong oxidizing agents as chromic acid and manganese dioxide and sulphuric acid on proteins. Casein, when treated with such reagents, yields, besides nitrites, aldehydes of benzoic and possibly propionic acids, whilst gelatin oxidized with chromic acid gives nitrites, hydrocyanic acid, and various fatty acids. Is it possible that a similar change occurs in the desamination of amino-acids in the body generally, and that such changes may also be represented in the way given above?

In conclusion, the writer would advocate the adoption of the term sulphaemoglobinaemia as the designation of this disease in place of the somewhat illogical and unsatisfactory name of 'enterogenous cyanosis'. The intestinal origin of this disease has been entirely disproved by the negative findings of various writers upon the subject, and the present work does not lend any support to this view. Further, the suggested title of 'microbic cyanosis' may possibly be found to fit the facts when our knowledge of this condition has been extended.

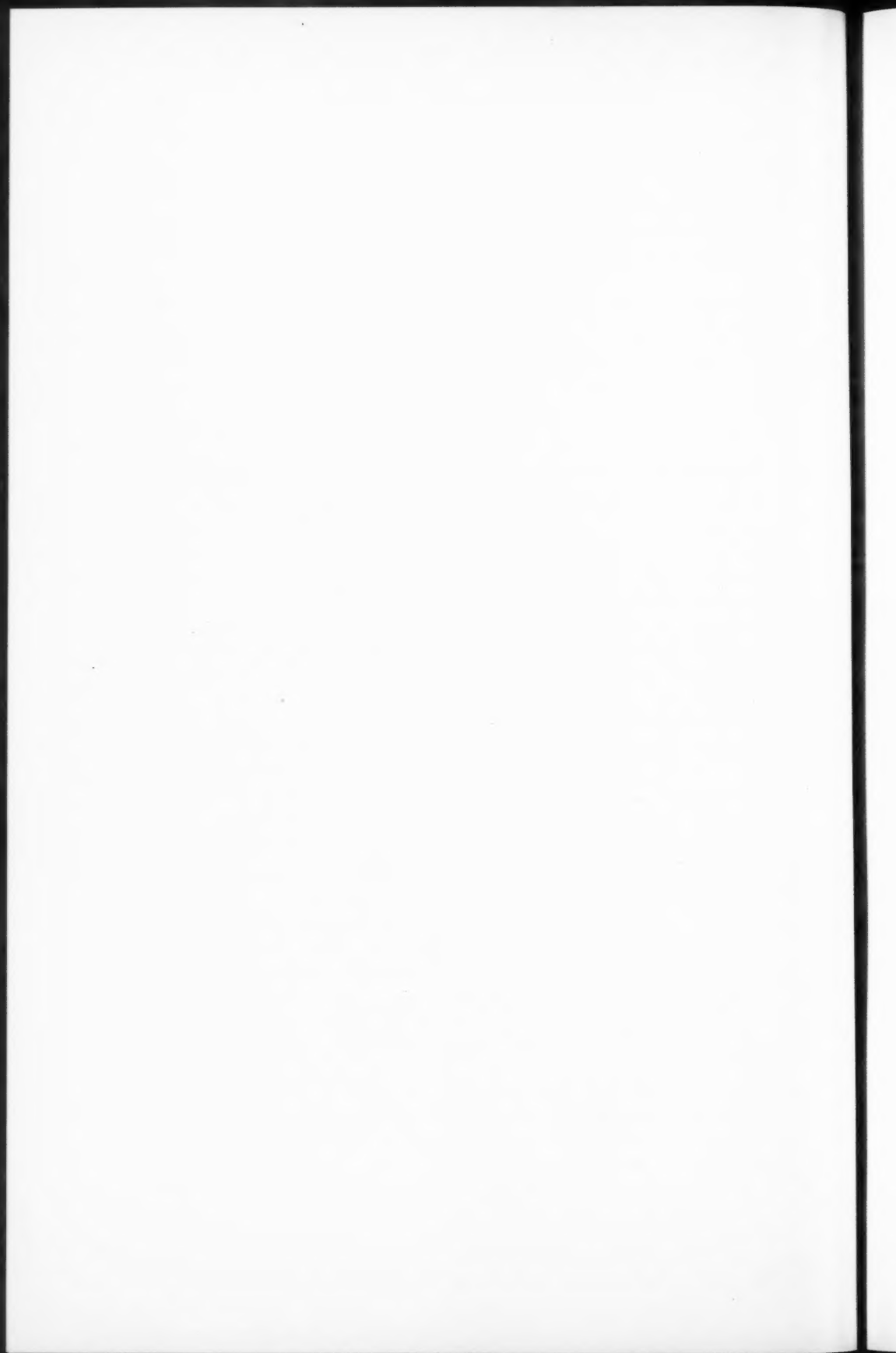
#### *Conclusions.*

1. The five cases of sulphaemoglobinaemia examined all showed the characteristic features of this disease, viz. marked cyanosis, weakness, headache, and constipation without signs of any lesion in the heart and lungs.
2. The sulphaemoglobin partially replaces the oxyhaemoglobin of the blood, and is present in the red blood corpuscles, and not in the serum.
3. The serum of all the patients contains a strong reducing substance, possibly of the nature of a hydroxylamine derivative capable of producing reduction of the oxyhaemoglobin. This is an essential and primary stage in the production of sulphaemoglobin.
4. A nitroso-bacillus occurs in the buccal cavity of these patients, and from its biochemical characters appears to be capable of producing such a reducing substance. The sulphuretted hydrogen present in the body is in sufficient quantity to form sulphaemoglobin under these conditions.
5. The prognosis of this condition is favourable when the primary cause is removed.

The writer wishes to express his indebtedness to the following gentlemen for kindly placing their cases at his disposal: Dr. Garrod, Dr. Samuel West, Dr. Essex Wynter, Dr. Jacob (Nottingham), Dr. Ernest Ringrose (Newark), and Dr. Steele (Stoke Ferry). For much valuable help and advice he would particularly thank Dr. Mervyn Gordon of St. Bartholomew's Hospital.

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# INTRACRANIAL SEROUS EFFUSIONS OF INFLAMMATORY ORIGIN

MENINGITIS OR EPENDYMITIS SEROSA—MENINGISM—WITH A NOTE ON  
'PSEUDO-TUMOURS' OF THE BRAIN

BY W. B. WARRINGTON<sup>1</sup>

(From the Medical School of Liverpool University)

With Plate 8

*Introduction.*

FROM time to time the clinical observer is confronted with patients who on the one hand present acute and alarming signs of intracranial disease or on the other hand more chronic manifestations of increased pressure within the skull. The course of the disease or the evidence from the post-mortem shows that the cause of the symptoms is not due to the commoner form of meningitis or to cerebral tumour, and a less known pathology has to be sought for. Complete or partial recovery is the rule in the acute cases about to be related, whilst the more chronic not infrequently terminate fatally, and hence their pathology is better understood. The writer submits that the explanation of the symptoms is not uncommonly the occurrence of a serous effusion within the skull. This and other pathological causes have been considered by many who have written about the same group of cases. An adequate examination of the various views put forward would lead to a discussion of some of the more obscure cerebral lesions. This has not been attempted, partly because it seems that sufficient data are not yet available to reach a final conclusion, and partly because the range of possible explanations is so wide.

The writer fully accepts the fact that serous effusion within the skull, like that within the thorax, is merely the manifestation of some primary pathological process, but pressure within the cranial cavity is the proximate cause of many grave cerebral symptoms and requires relief independently of its origin.

The hypothesis of fluid pressure has been proved to be correct in a number of cases, and deserves at least to be considered in others.

<sup>1</sup> I wish especially to acknowledge my indebtedness to Dr. John Owen, who has placed valuable material at my service, and also to Dr. Percy Marsh and Mr. Hugh E. Jones for permission to mention cases under their care.

*Historical.*

The chief landmarks in the history of our knowledge of serous effusion within the brain cavity, if we exclude congenital hydrocephalus, which was known to the ancients, may here be summarized. Robert Whytt, in 1768, described an acute fatal affection in children, associated with distension of the ventricles of the brain with serous fluid, causing hydrocephalus, and the ultimate recognition of this condition as tuberculous meningitis was made by Papavoine in 1830. Rilliet's paper, in 1847, dealt with a girl, aged 10½, suddenly taken ill with headache, vomiting, and convulsions, followed by progressive mental enfeeblement, and dying in four months. The ependyma was found in a gelatinous condition and the ventricles filled with serous fluid; the arachnoid and the pia mater did not participate in the inflammation. This appears to be the first recognition of a 'simple' effusion. Quinke, in 1891, introduced his method of lumbar puncture, and his papers 'Ueber Meningitis serosa' appeared in 1893 and 1897. He described seventeen cases, occurring suddenly in children and young people, with an onset of severe cerebral symptoms; the majority recovered, but there were seven post-mortem examinations. In none of them was there any purulent exudate; in all the ventricles were dilated; the ependyma was normal in one, thickened in two, and granular in appearance in three. No microscopic examinations were made.

Georg Boenninghaus, in 1897, analysed twenty-eight cases, and considers that in all the diagnosis was established either by the post-mortem or because they were permanently cured by operation. He recognized the infective origin of the condition and described the clinical symptoms. F. Schultze, in 1901, gave a full review of the recorded cases up to that date. Pierre Merle, in 1910, gave a full bibliography, and sought to prove that in many cases of serous effusion the chief lesion is to be found in the ependyma. To these may be added Connal's 'Study of the Cerebro-spinal Fluid', 1910, and Kopentzky's paper on 'Meningitis', 1912, which focus attention especially on the characteristics of the cerebro-spinal fluid in the inflammation of the meninges.

*Morbid Anatomy.*

It is not easy to classify and describe the morbid lesions which cause the serous effusions. The object of the writer is to give a review of the chief facts of that group of cerebral cases in which the excessive accumulation of fluid is of inflammatory origin, constitutes the most striking pathological appearance, and is the most important cause of the symptoms. It is possible that the excess of fluid found within the cranial cavity in some cases of heart and renal disease is partly inflammatory in origin. Such conditions will not be considered here. Thrombosis of sinuses and of the veins of Galen is attended by local exudations. In such cases the thrombosis constitutes the important pathological fact and the clinical problem of diagnosis and therapeutics is a different one. The part played by syphilis is also, except incidentally, excluded from the review.

Of the twenty-eight cases collected by Georg Boenninghaus, post-mortem records are given of twenty-one. Boenninghaus divides these into two groups: (a) Meningo-encephalitis serosa acuta. The brain and meninges, rarely either alone, are the sites of a serous exudate. Ventricular effusion, if it is present, is insignificant. Death follows the inflammation of the brain elements. Clinically the condition is malignant. (b) Meningitis serosa interna (ventricularis) acuta. The ventricles are distended with a serous exudate. Participation of the brain and its membranes in the inflammatory process, if present, is insignificant. Death is due chiefly to increased intracranial pressure. Clinically the condition assumes a benign form. Very exact accounts of the microscopical changes in the brain tissue, the blood-vessels, the meninges, the choroid plexuses, and the ependyma are given in many of the records, but the participation of the inflammatory change varies in the different tissues as indicated by Boenninghaus's classification.

The central thesis of Merle's work is that the lesions of the ependyma are the chief pathological basis of inflammatory effusions, and these he classifies as purulent and sero-purulent, serous, tuberculous, syphilitic, and chronic. We are here only concerned with the second of these groups, ependymitis serosa. It occupies an intermediate position between the acute purulent and sero-purulent inflammations on the one hand, and certain chronic ones where the inflammatory character is not so much in evidence, and which have no clinical significance. The table appended, from this thesis, displays very clearly the relationship between the anatomical lesions and the general nature of the symptoms.

*Lesions found in Serous Effusions of Inflammatory Origin with Signs of Intracranial Hypertension.*

	Diffuse inflammatory lesions (as Beck's case).	<div> <div>Encephalitis.</div> <div>Lepto-meningitis.</div> <div>Choroiditis.</div> <div>Ependymitis (often predominant).</div> <div>Meningo-ependymitis.</div> </div>
Bilateral, acquired ventricular hydrocephalus.	Choroiditis?	
	Ependymitis.	<div> <div>Generalized lesion of the ventricular walls (Parkes Weber).</div> <div>Localized, obliterating aqueduct of Sylvius, the fourth ventricle.</div> </div>
	Phlebitis of sinuses of the dura mater.	
Unilateral hydrocephalus.	Ependymitis obliterating the foramen of Monro.	
	Ependymal adhesions isolating a part of the ventricular cavities.	
Sero-meningitis.	Inflammatory oedematous distension of the arachnoid membrane.	Generalized.
		Localized (external pseudo-tumour).

Although the preponderating lesion is found in the ependyma, yet there is often associated with this encephalitis, inflammation of the choroid plexuses and non-purulent forms of lepto-meningitis, and the serous effusions which accompany these conditions may give rise to oedema of the brain itself, in addition to serous fluid in the meninges. Merle lays great stress on the perivascular infiltration, and especially upon the adhesive fibrous phlebitis in the veins of the

ventricular walls; these veins, together with those of the choroid plexuses and other collaterals, unite to form the small veins of Galen, which, directed backwards, ultimately form the single vein, the great vein of Galen. Obliteration and compression of the veins of Galen cause a well-known form of hydrocephalus, and it is easy to understand how this may also result from the lesions of the radicles, which Merle so carefully describes.

In the majority of the cases the hydrocephalus is bilateral; sometimes only one lateral ventricle is distended. The foramen of Monro may be found blocked by inflammatory tissue, or the aqueduct of Sylvius closed by adhesions, and in this case the hydrocephalus may be limited to the fourth ventricle. The foramina of Majendie, Key, and Retzius may be found blocked, but this is not an essential factor in the production of hydrocephalus, for excessive secretion together with diminished absorption may permit the distension of the ventricles to occur. The account given of the lesions found shows, therefore, that the excessive formation of fluid within the cranium, which entitles the condition to separate clinical consideration, is the result of inflammatory lesions of various structures, hence the names of meningitis serosa, ependymitis serosa, encephalitis serosa, by which cases have been described.

The pathological process may be acute with corresponding symptoms, or of a slower evolution when the symptoms are mainly those of chronic intracranial pressure. The more acute cases may become quiescent and the stormy onset abate, to be followed, perhaps, at a very distant period of time by signs of gradually progressive increase of intracranial tension, or a chronic lesion may be lit up and more acute symptoms supervene.

Fluctuation in the severity of the symptoms is a very characteristic clinical feature, corresponding partly to the amount of fluid present, and there seems evidence that the latter may be absorbed either wholly or in part.

The terms meningitis serosa, &c., like the expression pleural effusion, are only of clinical significance, and should be reserved for cases in which it may legitimately be concluded from post-mortem findings, or the clinical history, that fluid pressure was the chief cause of the symptoms.

Detailed descriptions of the pathology of numerous cases are given in the monograph of Boenninghaus, and by F. Schultze. Many references are given by Merle and Chabbert, and original records in the papers of Oppenheim and Nonne. A valuable paper with a record of a case is Tillgren's description of obliterative ependymitis of the fourth ventricle. Microscopically the thickening consisted of granulation tissue, vessels, and large giant cells in different places. No bacteria or spirochaetes could be demonstrated, and though the patient had suffered from a dry otitis, Tillgren did not consider he could connect the ependymitis with this. There was no evidence of syphilis. Parkes Weber gives the record of a case with a microscopical examination and a criticism on the pathology of the condition. Gerhardt described a cystic formation in the fourth ventricle with hydrocephalus; Spiller and Allen a congenital closure of the aqueduct of Sylvius; Warrington a thickening by granulation tissue of the

floor of the fourth ventricle, as the only lesion in a case of intense hydrocephalus of all the ventricles. Von Kalden and others have described the inflammatory reaction of the ependyma with hydrocephalus, in infection of the ventricles by the cysticercus.

*Pathogenesis and Aetiology.*

These cases are clearly inflammatory, though the causal organism may escape observation. The commonest associated condition is otitis media, and it is here that the practical problem of the diagnosis is of such great importance. In such cases there is a pus focus on the outer side of the dura mater, and it seems that it is reasonable to suppose that the toxins but not the micro-organisms penetrate this barrier; an analogous condition is seen in the other serous membranes, e. g. a sub-diaphragmatic abscess may cause a serous effusion into the thoracic cavity.

The paths of the encephalic infection are of great interest, especially to the aural surgeon, as a guide to surgical treatment, and this subject has recently been fully discussed by Tylor, from an analysis of thirty-six post-mortem records of serous meningitis. He shows that labyrinthitis is often present, and this may be the explanation of the nystagmus observed as a symptom in many of the recorded cases. Although the fluid withdrawn for diagnostic or therapeutic purposes is characteristically sterile, it must be remembered that micro-organisms of attenuated virulence may be present, and in fact the pneumococcus, typhoid bacillus, and streptococci have been found in the clear fluid so removed. Kopentzky discusses in detail the pathogenesis of the hypersecretion of fluid in meningitis, and when treating of serous meningitis maintains that the inflammatory exudates are merely manifestations of the same pathological process in differing stages of intensity. He quotes with approval Koerner, who summarizing, says: 'When micro-organisms or pus, arising either from the middle ear, the labyrinth, or the mastoid process, or from an extra- or intra-dural abscess, or from a brain abscess, or sinus thrombosis, reaches the meshes of the pia it does not always follow that the pia mater immediately becomes affected. Organisms of low virulence can propagate in the subarachnoid space and spread in the cerebro-spinal fluid to the ventricles and to the cord. The toxic substances produced by their growth, acting as irritants, cause an increase in the leucocytes in the cerebro-spinal fluid, and also may produce symptoms which can hardly be differentiated from a fully-developed meningitis. Such cases at autopsy do not show inflammatory changes or pus in the meninges. . . . Without doubt we are here dealing with a very early stage, the initial stage, of purulent lepto-meningitis.'

We have seen also that neither Boenninghaus nor Merle admit any essential difference between those cases which go as far as suppuration and those in which the exudate remains serous. The termination, however, of the inflammatory process in the 'serous' stage is the all-important clinical fact.

Besides otitis, many other pyogenic foci have been described, e. g. from



the nasal sinuses by Herzfeld, or from a distant site, e. g. in the pelvis or appendix.

The symptoms may also arise in the course of many of the general fevers, especially influenza and measles, typhoid, pneumonia, rheumatism, and erysipelas. Gastro-intestinal infections are mentioned by all writers, and Baginski considers that acute hydrocephalus occurs in infants in such diseases as bronchitis and whooping-cough.

The relationship of tuberculous infections to serous effusions into the cranial cavity is important. The ependyma is often inflamed in tuberculous meningitis. Merle figures these lesions containing both giant cells and bacilli.

It is, however, probable that the toxins of the bacilli from a distant site, or even the bacilli themselves with attenuated virulence, may cause lesions of the ependyma and hyper-secretion of fluid. In Quinke's early study several such cases were mentioned, and in one case, which survived eleven months, pulmonary tuberculosis was present, but the brain and meninges were free. There was great hydrocephalus and thickening of the ependyma.

Poucet and Lérique pertinently ask, Why should not the meninges be exposed to attenuated and slightly virulent infections like other serous membranes? 'The attitude of the diagnostician in the past has been to alter the diagnosis of tuberculous meningitis if the case recovers, invoking such conditions as syphilis to explain the symptoms; but why should the meninges be exempt from sudden oedema or fluid effusions leading to alarming symptoms, but susceptible of complete disappearance? The anatomical picture of meningitis can extend from transitory congestion to confluent tubercles, and its clinical course may extend from a passing headache to a fatal coma.' They admit the absence of pathological proof owing to recovery, but state that in four of these examples bacilli were found in the cerebro-spinal fluid. In some cases no definite etiology can be traced, but Merle has shown that the ventricles can be experimentally directly infected by injection of organisms into the blood-stream.

So far we have been able to adduce evidence that anatomical changes in the meninges, brain, or ependyma may be the cause of excessive secretion of inflammatory fluid. There is, however, a large group of cases in which we can only rely upon clinical evidence of excessive pressure in the cranial cavity, due to serous fluid. The evidence is the occurrence of the well-known symptoms of hypertension, followed by complete cure, and the clinical examination of the cerebro-spinal fluid. Briefly, in such cases the cerebro-spinal fluid is clear, sterile, and under pressure. Now it is precisely to this combination of symptoms occurring in many infective conditions that Dupré in 1894 gave the name of meningism.

F. E. Tylecote, in a paper on meningism, says that this may be tentatively defined as a 'functional' condition caused by the selective action on the meninges and cerebral cortex of the toxins which are circulating in the blood-stream.

The evidence we have adduced shows that serous meningitis and ependy-



mitis are organic conditions caused by the toxins or possibly attenuated organisms in the blood-stream. It is to be admitted that the clinical picture does not help much in a diagnosis between the two conditions, and we are left therefore to a study of the cerebro-spinal fluid and the attempt to discern whether it shows inflammatory characteristics or not. It appears to the writer that just as there is no essential difference between the pathogenesis of purulent meningitis (or ependymitis) and serous meningitis (or ependymitis), so there is no true pathological demarcation between 'meningism' and 'serous meningitis', though the examination of the cerebro-spinal fluid is the most valuable means at present that we have in determining the degree to which the processes have arrived.

Lastly, there is a group of cases of serous effusions in the cranium, of practical importance, in which the pathogenesis is obscure and the inflammatory origin doubtful.

Non-microbial toxins, especially alcohol and lead, have been mentioned as causes of inflammatory lesions of the ependyma. With regard to alcohol the evidence is doubtful; it is, however, well known that lead may cause marked signs of increased intracranial pressure, and Merle quotes some experiments on rabbits poisoned by lead, in which obvious lesions of the ependyma were found. Chabbert, in a Paris thesis on 'Des Réactions méningées aiguës aseptiques', describes the occurrence of meningeal symptoms after stavaine injection into the spinal theca, with the presence of a large number of multinuclear leucocytes in the cerebro-spinal fluid.

Injury to the skull is often mentioned as an antecedent in cases of acquired hydrocephalus, so much so that Oppenheim and other authors lay stress upon this history in the diagnosis of the condition.

It is certain that in 'concussion of the brain' there are often organic lesions such as lacerations of the brain, and the coincident vascular changes may form the anatomical basis in such cases.

Very mysterious are the well-authenticated cases in which apoplecticiform symptoms have rapidly come on, in apparently healthy persons, after severe psychical shock, and in which the post-mortem has revealed distension of the ventricles with serous exudate and acute ependymitis. To such cases the name serous apoplexy seems applicable as a clinical description; but 'apoplexia serosa' is a very old name. It was used to indicate the cause of death in old persons who died in a state of coma, and in whom nothing was found to explain the cause of death except hyperaemia and some excess of fluid. Gowers in his *Manual* writes: 'It (apoplexy) probably results in rare cases from congestion of the brain, although far less frequently than was commonly supposed. A similar condition may come on in the old without any visible lesion by which it can be caused. This has been termed "simple apoplexy". In the old the brain is shrunken, the convolutions are small, and the spaces between them are occupied by serum. Before this fact was recognized, undue importance was attached to this serum in the cases of "simple apoplexy"; it was thought to be the cause of the symptoms, and the condition was termed "serous apoplexy", a disease that has no real

existence.' Rokitansky considered, however, that this affection is in a great part identical with the inflammatory serous exudate already described. I have recently made a post-mortem on an old man who rapidly became comatose; little was found except some excess of fluid in the cranium, the kidneys and vascular system being healthy.

Insolation is mentioned by Oppenheim as another rare cause of acute hydrocephalus, and Gowers mentions this as a cause of active congestion, which may or may not go on to inflammation.

In the clinical section of this paper I shall mention an unusual state of coma in which the only etiology appeared to be exhaustion and exposure, and in which the cerebro-spinal fluid was removed under obvious pressure, indicating cranial hypertension.

#### *The Cerebro-spinal Fluid in Serous Meningitis.*

Observations of the cerebro-spinal fluid in various forms of meningitis are now very numerous. Kopentzky records the results of elaborate chemical analyses, and an examination of no less than a thousand specimens (chiefly from meningococcal meningitis) formed the basis of Connal's valuable paper. The condition of the fluid in serous meningitis has not been observed in nearly so great detail; the chemical analysis in particular has been neglected.

The most important chemical reactions which have at present practical significance are the degree of the alkalinity of the fluid and the fate of the carbohydrates (galactose). Both Kopentzky and Connal agree that the alkalinity is most diminished in the early stage of acute pyogenic meningitis and somewhat lessened in tuberculous meningitis. Kopentzky gives a table of exact estimations of the degree of alkalinity, in terms of known acidity, whilst Connal relied upon a simple colour test with plenolphthalein. I have not yet met with any precise statements regarding this point in cases of serous meningitis. The same writers emphasize the fact that the pyogenic organisms rapidly break up the sugar of the cerebro-spinal fluid with the formation of lactic acid, so that the determination of the sugar reaction and the alkalinity go hand in hand. Hence, as Connal says, the absence of sugar is pathognomonic of meningitis (pyogenic); on the other hand, most cases of tuberculous meningitis reduce the copper solution. Observations on these two determinations should therefore be of great value in deciding whether or not pyogenic organisms have actually invaded the intradural tissue. I am not able to find, however, many records on this subject. Kopentzky mentions that sugar reduction *was* present in four cases of meningism, three of 'hydrocephalus', and one of otitic sepsis with meningeal symptoms.

Tylecote mentions the case of a boy aged 10, a typical case of typhoid fever, who developed meningeal signs; he states that the fluid was absolutely clear and contained no albumin, but did *not* reduce Fehling's solution. I regret that in my own cases this point was not definitely observed. It seems that more precise records of the fate of the sugar are desirable. The testing should be made with

accuracy, for if loosely performed, there is some room for an error of the personal equation. The amount of sugar varies in the normal fluid. The destruction of the carbohydrate also must depend on the virulence, nature, and duration of the infection. It is well known that the meningococcus gradually loses its power of destroying the carbohydrate, but in the early stages a single observation may be fallacious. The most ready means to be certain if the copper solution has been reduced is to centrifuge the fluids.

Other characteristics of the fluid have been better studied; it is clear, sterile, and usually obtained under pressure. It may contain albumin slightly over the normal; often the cell elements do not exceed the normal, but lymphocytes in considerable numbers may be present, and sometimes the polynuclear leucocytes. Chabbert lays stress upon his findings that when the fluid is sterile, the leucocytes are found with a well-preserved normal appearance; this he considers due to the absence of disintegration by phagocytosis.

As a rare occurrence the presence of organisms of attenuated virulence has already been mentioned.

It is to be remembered that sometimes the ventricles are closed from the spinal subarachnoid space by inflammatory adhesions, and in these cases the examination of the fluid by lumbar puncture may not disclose the condition existing within the cranium, and the serous fluid thus obtained may not definitely exclude purulent meningitis. It is only in infants that the fluid can be obtained directly from the ventricles. Organisms also have been obtained by ventricular puncture when the spinal fluid has been sterile.

To summarize: The examinations of the cerebro-spinal fluid are not inconsistent with the view that meningism, serous meningitis, or ependymitis, and purulent or sero-purulent meningitis are grades in an inflammatory process. Clinical, and in many cases post-mortem, evidence shows that the inflammation may not advance beyond a certain point, and the importance of the recognition of this hypothesis becomes urgent if there is to be any attempt to arrest the development of purulent meningitis by operation, as Haynes and others emphasize. Hence the earliest recognition of the changes in the copper-reducing power of the fluid and its diminished alkalinity is necessary.

#### *Clinical.*

The number and variety of cases recorded under the heading of serous meningitis is very great. It is impossible, within the limits of this paper, to refer to many of these. I propose briefly to mention some illustrative examples either from personal observations or recorded by others, and to add a few remarks on the clinical diagnosis.

These may be classified into, first, those acute or subacute in onset, resembling the more fulminating forms of intracranial disease; secondly, cases slower in evolution, but liable to exacerbations, and producing more the clinical features of cerebral tumour.

*Group I.*

I. *Associated with otitis media.* The onset of intracranial symptoms in a case of otitis media may be fulminating and the patient quickly die. In such cases the membranes are distended with serous fluid, and the brain is softened. This is the meningitis serosa maligna of Boenninghaus, and is probably merely the early stage of a very virulent purulent meningitis.

Goerlitz records such a case, a boy aged  $2\frac{3}{4}$ , who suffered from otitis media, and rapidly developed severe cerebral symptoms. An operation was performed, and a tense injected dura found. At the autopsy no purulent fluid was present, but encephalitis with enormously distended ventricles.

The general symptoms in otitic serous meningitis are—headache, disturbed mentality, paresis, aphasia, delirium, stupor and coma, spinal rigidity, variation in the pulse-rate, a slight rise of temperature, sensitiveness to noise, photophobia, unequal pupils and diplopia, choked disks, and retracted abdomen. It is obvious, then, that the diagnosis between serous meningitis, non-suppurative encephalitis, brain abscess, and sinus thrombosis or purulent meningitis is none too easy.

The diagnostic difficulties that confronted the early observers are well illustrated by a case of Joel's in 1895. A girl, aged  $11\frac{1}{2}$ , came under treatment for a fetid left-ear discharge; Stacks's operation was performed, and she soon got nearly well. Two months later she was suddenly seized with headache, vomiting, and convulsions beginning in the face. Joel diagnosed an extra-dural abscess, or an abscess in the brain mass. The intracranial cavity was explored, and the brain needled in various places, but nothing found. A fatal termination was expected, yet the patient completely recovered. Joel reports that at the operation the brain meninges and tissue were seen to be oedematous, and he considered, in discussing the case, that he had had to deal with a serous inflammation of the pia mater.

A few years later, in 1898, Waldvogel related an instance of a boy, aged  $3\frac{1}{2}$ , who was seized with high fever and a cough. The diagnosis was pneumonia, but no signs were ever found. On the fourth day, the child became aphasic, vomited, and was convulsed, the high fever continued, and both ears began to discharge purulent fluid. The temperature dropped next day; the middle ear refilled with pus and the fever returned; on evacuating the pus, the temperature again fell, and all signs cleared up, except the aphasia, which remained for eight days.

A second case of his was that of a boy, aged 4, who after measles developed a cough and fever; no physical signs were found, but in three days somnolence with convulsions occurred, and a spontaneous perforation of the membrane with purulent discharge. The symptoms disappeared rapidly, but two days later the perforation closed, then the temperature rose again, and the cerebral signs reappeared. The infected parts of the ear were surgically treated, and the patient gradually recovered.

In a third case, with otitis, there were nystagmus, paralysis of the face, and loss of sight. All these symptoms gradually disappeared.

In a fourth child, signs of meningitis were present, convulsions, rigidity, &c., but the child remained alive, and her head was seen to be enlarging. Death occurred in ten weeks. The autopsy showed, besides the double otitis, brain oedema and great distension of the ventricles, with a cloudy light-coloured fluid. There was pus in the tympanic cavity.

Since these earlier cases, many others have been recorded, but it may be useful to mention two further cases of quite recent date recorded by Fedor Krause. Writing of this condition of meningitis serosa, he says, 'I am of opinion that this process is nothing more than an inflammatory oedema which may be secondary to a pus focus. It may give rise to all the cranial manifestations of septic meningitis or abscess.'

A girl, about 19, with otitis. Paracentesis of the membrane was performed. All went well until three months later, when grave cerebral symptoms arose, pointing to a temporo-sphenoidal abscess. This was found, and the patient relieved, but in six months she became ill again, the symptoms being of a fluctuating character, finally pointing definitely to a lesion in the posterior fossa. This was accordingly explored, and a considerable amount of fluid liberated from the arachnoid cistern; at the operation the fluid was observed to collect rapidly, forming a cyst in the middle line. The patient has remained perfectly well for a long time.

Another case, a child aged 5, was admitted with symptoms of meningeal irritation. There was a history of otitis eight weeks previously. Soon the symptoms indicated the temporal lobe to be the affected site. An operation was accordingly planned; after several failures to locate an abscess, clear fluid came away from the exploring cannula in considerable quantity. Krause considered that he had tapped a cystic collection in the substance of the brain, and that the fluid did not come from the ventricles. This procedure was followed by severe symptoms and convulsions, but improvement gradually occurred, leading to complete restoration of health. Krause observes that exposure of the temporal lobe or cerebellar hemispheres will show marked tension of the dura mater with no visible pulsation, but on perforation of this membrane a clear fluid will issue under pressure from the opening.

In the cases quoted, nearly all of which terminated in recovery, the evidence, partly clinical and partly from the operation findings, seems conclusive that the essential cause of the symptoms was an excess of serous fluid within the cranial cavity.

Four cases of some interest have come under my own observation. In three there was recent purulent otitis, and in one a history of ear trouble. The lack of notes with regard to the exact condition of hearing and labyrinth reactions is to be regretted, and the records are otherwise incomplete; one of the patients, however, was seen by Dr. McDougall, who satisfied himself that no direct surgical attack was desirable, and the state of another (Wilhelmina B.) was too acute to permit of observations of this nature being made. In all the symptoms were considered to be due to a toxin and not to microbial infection of the intracranial tissues. In three nystagmus was present, suggesting the possibility of labyrinthitis as the focus of the toxic invasion. In the first case to be mentioned, the operation findings indicated that excessive effusion of fluid was the chief factor in the causation of symptoms.

*Case I.* Wilhelmina B., aged 33, suffering from a slight offensive discharge from the left ear, was admitted on November 9, 1903, to the Stanley Hospital. The patient had been in excellent health, when, as she was undressing preparatory to going to bed, she was seized with headache and dizziness, and became unconscious. At midnight she was semi-conscious and constantly vomiting; when disturbed she would wake up, talk incoherently, complain of her head and vomit. If left undisturbed she would lie placidly without any stertor. The temperature was normal and the pulse 60. There was a right hemiplegia, including the face. The tendon jerks exaggerated, equal on both sides, but no plantar extensor response.

About 2 p.m. on the following day, the patient arrived in hospital; she was much livelier and better, and had even been out of bed in the interval. The hemiplegia had practically disappeared except for a droop in the face. She complained of headache over the frontal region, but soon relapsed into drowsiness if left undisturbed. There was some strabismus. The patient slept well during the night, and in the morning spoke intelligently. Temperature 99°. Pulse 60.

For the next two days there was still some drowsiness, but no vomiting and no hemiplegia beyond a very slight facial droop. Both optic disks were



blurred and congested, the change being most marked on the right side; slight nystagmus was noted, especially towards the right side. The general condition remained the same for the following days, with fluctuations in the degree of drowsiness and headache, the pulse rate being about 60.

On the 11th she was more wakeful and talked intelligently; occasional fits of restlessness were noted. The headache appeared to be postural, but always frontal in distribution. It was relieved by lying on the side; the dorsal decubitus or sitting up invariably made the headache intense. The temperature was normal except on two occasions, the highest record being 99.4°.

On the 16th (a week after the seizure) two small trephine openings were made into the calvarium by Mr. Douglas Crawford, one over the right temporal sphenoidal region, and the other over the right cerebellar region. The dura was bulged and there was no pulsation seen. On opening the dura the cerebral substance also bulged and a clear fluid escaped; congested vessels were noted. Exploration with a pus-seeker revealed nothing.

After this operative procedure the pulse attained a rate of 80, and remained generally at this rate until discharge from hospital. There was some pain and irritability the day following the operation, otherwise the post-operative course in the hospital was characterized by a steady improvement as regards the headache and mental torpidity. She left hospital on December 6, a fortnight after the operation and three weeks after the seizure, no symptoms of her illness remaining.

The sudden onset of stupor, slight convulsions and hemiplegia, with the detection of a mitral bruit raised the very natural suspicion of a cerebral embolism, but the rapid disappearance of the paralysis and the persistence of the stupor with intense headache, vomiting, infrequent pulse, and slight optic neuritis led to a search for another causal factor, and there was discovered a slight discharge from the left ear.

The question of cerebral abscess then arose, but failed to account for the clinical picture, the inconsistency lying in the very sudden seizure, and the rapid fluctuations of cerebral symptoms. The restoration to health on the evacuation of the fluid justified the exclusion of cerebral abscess in the diagnosis.

In the following three cases the nature of the pathological lesion remains more doubtful, and it is only suggested that the diagnosis of serous effusion had to be considered amongst other possible causes.

*Case II.* G. S., a boy about 13, had suffered from purulent otitis for seven months; there had until quite recently been a considerable discharge from the right ear, and a less copious discharge from the left. Dr. McDougall reported evidence of a recent perforation in the right membrane which was now healed. The boy complained of a severe frontal headache; for the last four weeks he had vomited many times and suffered from dizziness. The temperature and pulse were practically normal. There was marked optic neuritis on the right side, swelling = +3 with several haemorrhages and distinct small spots in the macular region, as well as larger exudations. The left eye showed less change.

Both pupils were large and equal and reacted to light and accommodation. There was nystagmus more pronounced on movement to the right, paresis of the left external rectus, and diplopia. No inco-ordination or affection of the gait or other nervous disorders. Urine, &c., normal.

The boy was only slightly drowsy, the tongue was clear and the bowels readily moved. Lumbar puncture showed a clear fluid under pressure, without cell elements and little excess of albumin. It was obviously a case of intracranial hypertension. The diagnosis lay between purulent meningitis, sinus thrombosis, abscess of the brain, and meningitis serosa. The absence of fever and the slight nature of the constitutional symptoms were against a purulent meningitis, which was also excluded by the nature of the cerebro-spinal fluid.



Sinus thrombosis, with which the lumbar puncture findings were not inconsistent, was also considered very unlikely on account of the absence of any local signs, and the mild constitutional symptoms. There remained for consideration abscess of the brain. Against this were the normal pulse, the clear tongue, state of the bowels, and the clear mentality. The physical signs did not indicate disease of those parts of the brain commonly the site of election in abscess from ear disease.

Further, the optic neuritis was of a very high grade, rarely seen in abscess. As Dr. McDougall's report indicated that no direct surgical attack was desirable, the diagnosis of meningitis serosa was made, and we decided to wait. The progress of the case justified this view, for the patient was discharged quite well in six weeks. Calomel at night-time, from time to time, was the treatment.

The symptoms here presented resemble closely those described by Gradenigo as sometimes present in acute middle-ear inflammation. He describes a well-known triad of symptoms in acute middle-ear inflammation—pain in the temporal and occipital region, bilateral abducens paralysis, and optic neuritis. Gradenigo's explanation is that the inflammatory process spreads from the middle ear to the apical cellular spaces of the pars petrosa.

The sixth nerve lies along the inferior petrosal sinus close to the tip of the petrous bone, and is separated from the apical pyramidal cells, when these exist, by a partition of bone which may in some instances be thinned almost to transparency or riddled with minute perforations. Gradenigo believes that inflammation or suppuration in this region is responsible for the paralysis of the sixth nerve, and has actually demonstrated this in several instances.

Hugh E. Jones, in 1898, fully described this symptom group in a case of mastoid disease and attributed the symptoms to a basal meningitis.

J. S. Barr, in 1908, related two cases associated with perisinus abscess and attributed the group of symptoms to a serous meningitis in the anterior cisterna. In the case I have just recorded a serous effusion seems a reasonable hypothesis on account of the absence of any grave constitutional symptoms, and affords an explanation of the entire disappearance of the severe optic neuritis and other signs without operative procedure.

Barr and Rowan have found that optic neuritis, uncomplicated by other grave intracranial lesions, occurs to the extent of 6.8 per cent. in cases of otitis media, and consider the most probable cause to be a meningitis serosa.

*Case III.* Isaac C., about 54, had suffered from double otitis for many years, and we found a foul discharge from the right ear; the left was dry. The patient told us that the otorrhoea had been very slight until about five weeks before, when the discharge from the right ear became copious, and that he then began to suffer from severe headache, vomiting, and mental disturbance. These troubles made it necessary for him to stay in bed.

The leading symptom was the slow mental responsiveness combined with disorientation in time and space; he said he was in Wavertree, whereas he was in the hospital. He did not know his age and could not recognize those who were constantly in attendance on him. The pulse varied from 80 to 100, and the temperature remained for three days at 98°—on no occasion was over the normal. There was slight optic neuritis, but no signs pointing to a local lesion were discovered.

We felt anxious about this man, for a patient with a cerebral abscess may slip away whilst under observation, and even when this is provisionally diagnosed. Accordingly Mr. R. W. Murray was asked to take the matter in hand. He cleared out the offending regions of the ear on both sides, and finding no cause to proceed as far as the dura by the direct route, he explored both temporo-sphenoidal lobes also with negative results. The symptoms very slowly disappeared, and some months afterwards we saw the patient quite well, and cured of his otorrhoea.

*Case IV.* Gwilym W., aged 17, admitted to hospital on May 16, 1912, complaining of right frontal headache and pain down his left side, with weakness and hyperaesthesia of this side, a left extensor plantar response, and a pulse-rate of 55, gave the following history: On May 7, retiring for the night, his left arm felt 'queer'; he woke up next day with some numbness and weakness of the arm, and a few hours later he noticed the left leg also weak. Vomiting and right frontal headache supervened.

On examination his left arm and left side of the face were found to be weak, and there was hyperaesthesia of the left side with left extensor plantar response. Slight double optic neuritis was noted.

The pupils were unequal and varied, the right usually being larger than the left, but occasionally the reverse. Vomiting occurred suddenly and unexpectedly and without nausea. There was slight stupor. The temperature was normal. The pulse-rate for the first few days averaged 50, the lowest recorded being 46. There was slight nystagmus.

He told us that eight months previously he was 'off work' for three months with ear trouble. In the course of a month he gradually lost all these symptoms, and remains well up to the present time.

*Diagnosis.* The labyrinth (and the toxic infection of the subarachnoid fluid by the perilymph) may be the primary site leading to infection. This can only usually be proved by special aural tests, though it appears to be a frequent cause, and may be suggested by nystagmus.

A sinus thrombosis may occur, and if the infection is of a low virulence an inflammation and fluid exudate due to toxæmia only may result. Such a thrombosis may become organized and the blood-flow re-established by canalization. Unless this is revealed by operation, or indicated by local signs and a fever of sepsis, it seems impossible to diagnose such a condition.

From non-suppurative encephalitis the diagnosis may also be very difficult or even impossible, for the infective agents may be the same. We rely chiefly, as indications of encephalitis, on the prominence, permanence, and early appearance of focal signs, and often the febrile onset perhaps attended by rigors.

It is the differential diagnosis from abscess of the brain that requires the most urgent answer; the chief guiding marks seem to be: (1) The abrupt onset. (2) The fluctuating course of the symptoms, alternations of somnolence and clear mentality, and variations in degree of the optic neuritis, especially recognized in the veins of the papilla. The transitory duration of the paresis which may be present. (3) The absence of certain constitutional signs often associated with brain abscess, for example, anorexia, the foul tongue and breath, the intense torpor of the bowels, and the depression of the pulse-rate and the temperature. (4) The localizing signs of the brain mischief may not be those commonly found in otitic brain abscess.

*II. Associated with tuberculous lesions.* Some of Quinke's cases have been quoted, in which a post-mortem revealed a definite ependymitis with hydrocephalus. Many such cases terminate favourably and the presence of definite anatomical lesions can only be surmised. Poucet and Leriche cite a striking example: A woman, aged 36, with tuberculous arthritis of the elbow; resection:—five days later vomiting, convulsions, coma. Fatal prognosis given by the physician; complete recovery of the patient. Five years later

tuberculous disease of os calcis; this was also resected; meningeal symptoms returned in less violent degree, i.e. intense headache, photophobia, delirium, tremor, and constipation, and again complete cure.

A similar case was that of a young girl under my care, who was admitted with high fever, somnolence, pains in the head and joints, and Kernig's sign. The face was markedly oedematous, and over the knees and elbows the skin was raised in localized red patches. Lumbar puncture showed a clear fluid under pressure. There was no albuminuria and the optic disks were normal. Over the right apex of the lungs signs of consolidation and râles were present. These signs were thought at first to be due to pneumonia, but the subsequent course showed that the case was one of tubercle, the bacillus being found in the sputum. All the cerebral signs disappeared.

Another case, under the care of Dr. John Owen, was that of a boy, aged 9, suffering from peritoneal tuberculosis with the supervention of meningeal signs, pyrexia, stupor, Kernig's sign, projectile vomiting, headache and irritability, paresis with inability to stand. The child recovered in three months from the cranial symptoms and the abdominal signs improved. He died many weeks later from exhaustion ensuing on faecal fistula, &c., but perfectly free from meningeal symptoms. At the post-mortem the brain and meninges appeared normal.

III. *Associated with the specific fevers.* Examples of these are very numerous; most of them are considered as illustrations of meningism. In the differential diagnosis some of the points mentioned by Tylecote are helpful: (a) Meningism is often but not always early in its occurrence and of short duration. (b) Kernig's sign is usually absent in meningism. (c) Pyrexia is more often absent in meningism than in meningitis. (d) Opisthotonus is a point in favour of meningism. (e) Marked involvement of individual cranial nerves is in favour of meningitis. (f) The occurrence for the first time in the defervescent or convalescent stage of an acute infective disease of symptoms of meningitis is very much against meningism. (g) The onset of meningism is acute, and the termination rapid. (h) Slowing of the pulse and irregular respiration are rare in meningism.

When the cerebro-spinal fluid has been examined in these cases, it has been found normal, with the exception usually of evidence of increased pressure. In a case under my care possibly the rheumatic toxin was a cause.

A young boy was admitted almost in coma, with retraction of the head and neck, marked Kernig's sign, and fever. There was no sign of lung disease, nor did the respiratory rate indicate pneumonia. The urine gave a slight indication of diacetic acid with ferric chloride.

Lumbar puncture showed a clear fluid under considerable pressure, without undue proteid content and devoid of cells. The signs and symptoms subsided in the course of a week. Some months after this attack, the boy was admitted again with typical erythema nodosum.

IV. *Injury to the skull* has been recognized as a cause by all writers on hydrocephalus. The symptoms usually come on gradually; thus in one case, recorded by Finkelnburg and Eschbaum, ten years after a severe head injury the patient began to show unsteadiness in walking and suffered from occasional headache, sometimes stiffness in the neck, loss of vision, vomiting, and weakness in the right arm.

Nine months later optic neuritis developed, and the eyes became prominent. The ventricle of the brain was punctured, and fluid recovered under high pressure; gradually all the symptoms subsided.

In a case of Nonne's, a woman, aged 29, three years before her fatal illness received a violent blow on the head, from which she apparently completely recovered, after suffering for six weeks from headache, vomiting, and dizziness.

But one month before admission to hospital these symptoms recurred, the gait became unsteady, and double optic neuritis developed; death came suddenly. At the autopsy nothing was found beyond great dilatation of all the ventricles, the ependymal lining being quite smooth.

V. Still more obscure are the cases which follow *mental shock*. Nonne mentions the case of a man, aged 30, who witnessed the death of his wife in a street railway accident; he immediately became collapsed and vomited. The next day there was violent headache, the pupils became immobile and dilated, double optic neuritis was present, coma supervened, and death occurred in twenty-four hours. The autopsy showed marked hydrocephalus and fresh granulations of the ependyma.

A similarly striking case was recently recorded by Armstrong. A man about 54, in previous good health, was knocked down by a bull. He was rather badly bruised, but more seriously frightened, as he thought he would have been killed. He was unable to return to his work, remaining in a very nervous state, apprehensive and anxious. The lips and tongue were often tremulous. At the end of four months the lower limbs became rigid; he was unable to raise himself to the sitting posture, but could walk fairly well. The mind became greatly affected, the expression vacant, his hands picking at the bed-clothes; evacuations passed involuntarily. The temperature remained normal until a bronchial catarrh supervened, ending fatally. At the post-mortem great dilatation of the ventricles was the only lesion found.

VI. *Starvation and exhaustion* possibly lead to a similar condition. I saw a remarkable case of this kind some time ago at the Cottage Hospital, West Kirby, with Dr. Thacker King. A young man was found comatose in a field in the district and removed to the hospital. He was emaciated and in evident poverty. I found him lying quietly in bed, normal pulse and slightly sub-normal temperature, pupils immobile and disks normal. There were no signs of meningitis or paralysis, no abnormality in the urine. The cerebro-spinal fluid was normal (the presence of sugar not tested for), but under pressure. Dr. King told me that he lay like this for twenty-seven days, and then came round and left the hospital, apparently quite well.

VII. Lastly, there is a series of cases described by Quinke in 1897, in which sudden and severe cerebral symptoms set in, such as headache, vomiting, and optic neuritis; all these were in young people. A number recovered under mercury, which Quinke recommends; in several no cause could be suggested. In one case the attack occurred after getting wet through, in another the patient was chlorotic, and in some others, chiefly in young women, Quinke considers that there was a cerebral effusion of serous fluid from altered vasomotor changes in the brain. These he calls *angioneurotic* in origin, and it is interesting to note that Quinke attributes many nervous and so-called neurasthenic headaches to this cause.

#### *Group II.*

A large number of cases are recorded in which during life the symptoms were those of hypertension, and often marked local signs, and in which a post-mortem examination revealed marked dilatation of some part of the ventricular system of the brain, without the presence of any tumour. The difficulty in diagnosis from tumour of the brain is great, and is discussed in considerable detail in Oppenheim's and Bruns's well-known text-books, and in other papers mentioned in the references. Three cases with post-mortem examinations, which present special features of interest, have come under my own observation.

*Case I.* Peter, aged 24, a miner, was sent to me by Mr. Hugh E. Jones, August 27, 1907. His present illness commenced nine months before with head-



ache; previously he had not suffered from any illness or injuries, and appeared to have been temperate. The pain in the head soon became more constant and severe, and was always felt in the left side of the head near the vertex. In five months he complained of double vision and staggering in walking, and noticed weakness in sight. These symptoms persisted, and two months before admission to hospital, vomiting began and increased in frequency.

*Examination on August 27, 1907.* The patient was well nourished; he walked like a blind man, and was found to be completely blind in the left eye, and to retain only power of perception of light in the right eye. The pupils were dilated and did not react to light. The eyeballs generally rolled slowly to the left and there was a marked lateral nystagmus, though, unlike what occurs in 'miner's nystagmus', the eyes were steady when directed upwards. There was complete loss of smell, slight left-sided facial palsy, and some diminution of acuity of hearing on the right side, but no sensation of noises in the head. No paralyses of other cranial nerves were detected. Muscular power in the limbs was fair, and there was no loss of sensation, tremors, or inco-ordination. The knee-jerks were absent, but other reflexes equal and normal.

Ophthalmoscopic examination showed that both disks were in a condition of post-neuritic atrophy, and numerous haemorrhages were present.

The headache and vomiting continued, though their severity varied. The viscera of the thorax and abdomen were normal.

The cerebro-spinal fluid withdrawn by lumbar puncture was examined, and did not appear as withdrawn by the needle as if under much pressure; it contained a few lymphocytes and rather more albumin than normal; the important finding was the presence of a Gram-negative non-motile bacillus, which was obtained several times and cultivated in pure culture. Mr. Keith Monsarrat explored the left cerebellar fossa on August 28, and found some evidence of pressure, but not very great. On September 25 the left frontal region was explored and great bulging of the brain was seen; on opening the dura about 3 oz. of cerebro-spinal fluid was removed by needle. The patient did not survive many days.

The post-mortem examination showed that the heart muscle was soft and its cavities dilated, the organ weighing 10½ oz., i. e. slightly over the normal; the valves were normal. There was no change in the arteries. The liver and kidneys were congested, otherwise normal; a few calcareous glands were found in the mesentery. On examining the brain, a small collection of yellow gelatinous fluid was seen in the arachnoid space, around the pituitary body and down the surface of the pons. The lateral ventricles, which were slightly dilated, contained rather an excess of a somewhat cloudy fluid, microscopically found to be due to a mixture of mononucleated and multinuclear cells. Neither the foramen of Monro nor the aqueduct was dilated. There was no tumour or vascular lesion in the brain, and the spinal cord when cut into small pieces appeared normal.

A microscopical examination of the hinder part of the brain was made, sections through the medulla, pons, and corpora quadrigemina being stained with haematoxylin, Weigert's and van Gieson's fluid, without demonstrating any abnormality, beyond perhaps some vascular dilatation and perivascular infiltration in the floor of the fourth ventricle. The pia mater appeared normal.

*Case II.* R. T., aged 39, a cow-keeper, on the advice of his medical attendant, became an in-patient of the Stanley Hospital on April 14, 1908.

The following history was elicited: He had been addicted to occasional drinking bouts for some years; during one of these lapses, a fortnight before admission, he attended a local race meeting, returning home in a dazed condition and complaining of the symptoms for which he was admitted, viz. swelling of the right knee-joint and occasional headaches, with stiffness of the back of the neck.

There had been considerable pyrexia during this period, and on the evening of his admission to hospital his temperature registered 103°. It gradually fell, after a remittent course, to normal on the eleventh day after admission. The effusion into the knee-joint subsided in the course of two weeks, but the headaches became more frequent, and were attended with vertigo. In the intervals between these paroxysms, he lay placidly in bed in a state of slight mental obfuscation.

He was a well-developed but spare man; there was general weakness, but no paralysis of the limbs: his gait was staggering. His headaches were mainly frontal, and in the vertiginous attacks he felt himself revolving towards the right side.

During his stay in hospital nystagmus in all directions developed, and for about ten days the right pupil was dilated and immobile. There was no vomiting and no optic neuritis. He was given potassium iodide in 10-gr. doses, with inunction of mercurial ointment. Under this treatment the intensity and frequency of his paroxysmal headaches became less marked, and he left the hospital on the 22nd of May improved.

On June 2 he was readmitted, with his previous symptoms greatly accentuated. The paroxysmal headaches became more frequent and intense, and reminded one of megrim. On June 5, while sitting up in bed, he was suddenly seized with vertigo and fell backwards in an unconscious state with stertorous breathing. The arms were jerked two or three times, but there were no general convulsions. The pupils were dilated and immobile, but the corneal reflexes were present. There was no marked change in the pulse. Consciousness returned with flushing of the skin and sweating. During the ensuing three weeks any disturbance or sitting up would bring on one of these seizures of varying severity, but generally less marked than the one described.

On the 24th of June, while the operation for lumbar puncture was in progress, one of these fits supervened and ended fatally in five minutes, the respiration stopping some time before the pulse-beat.

A further noteworthy feature of his illness was the slowly progressing left external ophthalmoplegia appearing soon after his readmission early in June; it became complete a week before his death. There was no optic neuritis, no tremor, and no sensory loss. The pupils were equal and reacted to light, though sluggishly. Towards the end of his illness his mental condition deteriorated and he passed urine in the bed. Post-mortem examination showed that, with the exception of the brain, the organs were normal. On moving the dura the arachnoid membranes were seen bulging outwards at the cerebellar pontine angles, and the tentorium cerebelli displaced upwards. There did not appear to be any meningitis or thickening of the membrane. On looking at the under surface of the brain, the basilar artery, as it lay on the pons, was deviated to the right of the middle line, and the left third nerve was seen to be shrivelled up to half the size of its fellow. A concretion the size of a pea occupied the site of the pineal gland.

On opening into the brain a large funnel-shaped dilation of the fourth ventricle and posterior part of the iter was found, but the lateral ventricles and the third ventricle were not dilated (see Plate 8).

Microscopic examination of various parts failed to reveal any abnormality, and the third nerve itself, examined by the Weigert and Marchi methods, did not show evidence of degeneration. The paralysis was apparently due to pressure.

*Case III.* Charles M., aged 34, was admitted to the Stanley Hospital in March, 1908, with a history of pleural effusion the previous summer, 32 oz. of serous fluid having been withdrawn.

He complained in hospital of intense headache and vomiting attacks, with



occasional vertigo. In appearance he was healthy, though his facial vessels were congested, giving him a bluish, bloated appearance. The hands were slightly tremulous when held straight out. Optic neuritis with haemorrhages was found especially marked in the right eye. In April an effusion into the right knee-joint developed; this and the headache disappeared while he was taking a mixture of sodium salicylate. There were no focal physical signs, and no signs of disease in the viscera, and the urine was normal.

He left hospital improved, but continued to attend as an out-patient. His headaches intermittently recurred and he became sleepy, and complained of pains generally in his limbs. He was readmitted to hospital, again improved, and was discharged. In October he fell in the street in a fit of vertigo, and remained unconscious for an hour. He was readmitted to hospital, and continued to get these seizures occasionally with convulsions. On lumbar puncture, clear fluid came out under pressure, and a short bacillus was cultivated. He again improved and was lost sight of until the Medical Officer of the Netherfield Road Fever Hospital communicated with us, last March, saying the man had been admitted for 'typhoid' and had died. Thus the remission of symptoms had extended over a period of four years. Post-mortem examination of the lungs showed signs of recent tubercle, and a kidney showed a number of miliary tubercles. A fairly thorough examination of the brain was made. To the naked eye it appeared normal; there was no hydrocephalus, no meningitis. Microscopical examination of the meninges, part of the cortex of the brain, and of the walls of the ventricles also failed to show any distinct abnormality.

The interesting features about these cases are the association with effusion into the synovial sac of the knee-joint (Cases II and III), so suggestive of a parasitic or at least a toxic origin, and the definite finding of a micro-organism (bacillus) which was cultivated on media (Cases I and III). A puzzling pathological feature in R. T. (Case II) is the limitation of the ventricular distension to the proximal end of the fourth ventricle and the iter, without any obvious occlusion of the passages and foramina at either end of the distension, and without any evidence of inflammatory trouble. The latter had no doubt resolved, and this supports the hypothesis that inflammatory action and fluid effusion may be responsible for the symptoms, even in those cases where the post-mortem examination reveals no trace of such. This may explain the negative finding in Charles M. (Case III).

#### *Circumscribed Meningeal Effusion.*

Placzek and Krause described such a case: the symptoms were vomiting, headache, enfeeblement of the gait, tendency to fall to the left, almost complete ophthalmoplegia of both eyes, and right facial paralysis; no change in the optic disks. The diagnosis was a tumour in the posterior cranial fossa. An operation was undertaken, but no tumour found; there was, however, widespread adhesion between the upper surface of the cerebellum and the tentorium, with great collection of the cerebro-spinal fluid in the space thus shut off. The patient apparently completely recovered in eight weeks.

Oppenheim and Borchardt relate a similar case; the patient was a little girl. Complete recovery, with the exception of some optic atrophy, followed the removal of fluid from the posterior fossa.

Raymond and Claude record a case in which the symptoms were due to a circumscribed collection of fluid over the cortex of the brain. Another case is recorded by Sarbó and Oppenheim: a man, aged 24, no history of syphilis or alcohol; he had suffered from recurring hemiplegia with epilepsy. At an operation there was found a local collection of fluid in the lepto-meninges over the Rolandic cortex.

In these examples it is possible that encephalitis was the primary lesion.

*Internal Hydrocephalus associated with Cerebro-spinal Rhinorrhoea.*

Sir StClair Thomson points out that cerebro-spinal rhinorrhoea is almost invariably accompanied by cerebral symptoms, and a remarkable case of this kind was described by Professors T. R. and E. E. Glynn. Professor T. R. Glynn says: 'There can be no doubt, in my opinion, that my patient suffered from acquired internal hydrocephalus, and that the spontaneous escape of the cerebro-spinal fluid relieved intracranial pressure and led to recovery.' However, this patient has since died, after a series of epileptic convulsions, and, owing to the kindness of Professor E. E. Glynn, I have had the opportunity of seeing the brain. It was a case of intense hydrocephalus, the downward pressure having been great enough to erode the sella turcica. Dr. John Owen informs me of another case under his care. Wm. C., aged 30, complained of headache, off and on, for three years, and of vomiting from time to time without nausea. Like Professor Glynn's case, he gave a history of an injury to the head at the age of 14, as was evident from the presence of a long transverse scar over the right forehead and right temple. For some time he had noticed dripping of fluid from the nose, so that he often had to use as many as a dozen handkerchiefs a day. He had well-marked nystagmus, and slight left facial weakness and some optic neuritis. There was some left hemiplegia, and both knee-jerks were increased. The fluid from the nose was not identified with cerebro-spinal fluid, but that was the supposition, and the case supposed to be one of internal hydrocephalus.

*Diagnosis between acquired Internal Hydrocephalus and Tumour of the Brain.*

Many writers, as for example Oppenheim and Bruns, consider that a diagnosis cannot certainly be made. It has, however, been correct in many recorded examples. It is important to remember that such a condition exists when confronted with an anomalous case of intracranial tension. The history, especially of injury to the skull, or a previous possibility of infection as from otitis, is important, and if the head is obviously enlarged, we may, in an adult subject, suspect early mischief in childhood. Undoubtedly also the remissions in the course of the disease as contrasted with the general steady uninterrupted progress of a tumour are important aids. Not merely, however, may remissions for long periods of time characterize the clinical history, but they may occur during the actual progress of the symptoms, either general or focal.

Oppenheim lays great stress upon the presence of fine tremors of the hands, or upon exophthalmos; most of his patients have been women who have complained of headache, vomiting, optic neuritis, paresis of the eye muscles, nystagmus chiefly to one side, and rotation of the head, noises in the ears, corneal areflexia or hyporeflexia and cerebellar ataxia, all to the same side. It is, however, certain that none of these signs are to be relied upon. If we consider that the pathology of the disease permits the conclusion that effusions may vary in amount from time to time, or even entirely disappear, some explanation of the diagnostic importance of the fluctuations and remissions is given.

A fairly constant symptom is the loss of the knee-jerks, possibly due to pressure within the spinal theca, and I have in several instances met with cases of long-continued 'neurasthenia' with this sign, that has made me suspect some

increased intracranial pressure as the pathology; indeed Quinke long ago offered such an explanation of minor cases of headache and neurosis.

*On certain cases of Intracranial Tension of unproved Pathology.*

The cases discussed, which have been shown in many instances to be examples of acquired internal hydrocephalus, form one of the group sometimes called 'pseudo-tumour of the brain'. Except as an acknowledgement of ignorance this term should be discarded. In a brief review, and for practical purposes, I shall classify these as follows:

1. *Cases, chiefly in children, in which all symptoms of intracranial pressure disappear for an indefinite time, perhaps permanently, without any special treatment.*

I have notes of four children who suffered from marked general signs of intracranial pressure, and who all completely recovered, and were known to be well several years after the illness.

Mary C., aged 10, under the care of Dr. Percy Marsh, admitted to hospital May 19, 1903, with vomiting, headache, and marked double optic neuritis, vision being equal to 6/60. The disease was afebrile; there was no septic focus, and apparently no reason to suspect either tubercle or syphilis. On Oct. 29 the child appeared absolutely well, and Mr. Chas. S. Shears was unable to find any trace of optic neuritis. The treatment was cod-liver oil and syr. ferri iodidi.

Joan H., aged 3½. A fairly well nourished child. First seen in January, 1912. For some weeks the child had been ailing, and had made complaint of pain in the abdomen, and stools recently had been loose and offensive. For the last two weeks vomiting from time to time had been a symptom. There was a deflexion of the head towards the right shoulder. There was obvious bilateral abducens paralysis, and intense double optic neuritis. No other signs of nervous disease discovered. No septic foci, temperature and pulse normal. This child gradually completely recovered and is known to be quite well at the present time.

Edward S. and Ada W., whom I had the opportunity of watching, were two other young children under the care of Dr. Percy Marsh. In both there were double optic neuritis, vomiting, and headache, but no focal signs. No focus of disease could be discovered, and there was no fever. Both apparently completely recovered, and were watched for many months.

These children may have had a solitary tuberculoma in the brain, but such tumours usually leave some damage behind. Sinus thrombosis is another possibility, but the absence of a cause, or of the asthenia and partially comatose state which usually accompany primary non-phlebitic thrombosis, seems to militate against this explanation. I suggest that a possible cause may be serous effusion into the ventricles, though the nature of the infection cannot be discerned. Encephalitis may have been the lesion, and a fluid effusion secondary to this. Encephalitis, as it is recognized clinically, is usually a febrile and more stormy disease with focal signs. Spiller has, however, recorded a case of a girl, aged 14, in which polioencephalitis proved by operation to be the lesion, and, associated with optic neuritis, greatly resembled the clinical picture of tumour. Focal signs were, moreover, marked.

Oppenheim has drawn attention to the recovery in children from tumour-like symptoms. He records six cases: Boy, aged 17, with 'fits', known to be well three years later; boy, aged 10, 'fits' and monoplegia, known to be well in two years; girl, aged 13, paresis of arms and face; boy, aged 8, right facial paralysis, known to be well in eight months; and boy, aged 6, right-arm paresis, known to be well eighteen months later.

In four of these cases optic neuritis was present, in all headache and vomiting, and all were afebrile affections. Strumpell quotes similar cases in his text-book. Oppenheim considers the symptoms due to—circumscribed tubercular encephalitis; a chronic form of encephalitis, of unknown origin; or to an unknown pathological causation.

*2. Cases in which recovery, partial or apparently complete, rapidly follow a simple decompression, and in which the patients are known to be alive and well for at least many years after the operation.*

It is well known that certain tumours of the brain may cease to grow or undergo retrograde change with the apparent disappearance of all symptoms; such tumours are especially the cholesteatoma, angioma cavernosum, aneurysms, the cysticercus, and the solitary tubercle; but the relative frequency of the group now under consideration seems to exclude such an explanation as of general applicability. Of twenty patients recently under my care submitted to operation for tumour-like symptoms, in four the diagnosis of internal hydrocephalus was considered possible or probable. These four had marked general symptoms of intracranial pressure, but no focal signs. In two a bilateral posterior decompression was performed.

C. S. rapidly recovered her general health, and was able to go about her work under observation a year. Complete blindness supervened.

M. B. was also alive and well three years after the operation; complete blindness in one eye, vision in the other practically perfect.

In another case, G. H., the decompression was on the right side over the cerebrum; the patient was known to be alive and well, but with marked defect in vision, five years after the operation.

K. B., three years after cerebral decompression, has no symptoms, and vision has been restored from  $\frac{5}{32}$  and  $\frac{5}{64}$  to  $\frac{5}{8}$  in both eyes.

These patients were frequently seen. No further symptoms occurred, and no hernia developed. Such immunity is unlikely had a tumour been present.

In a series of thirty-five cerebellar exposures recorded by Cushing, nothing was found in eleven, and other operators have recorded a similar experience. Cushing reports that it was just this group of cases which did very well; many were known to be alive and well months after the operation. Spiller and Frazier suggest that some of these cases are examples of meningitis serosa.

A suggestive case was recently under the care of Dr. John Owen, Jan. 1912: a boy, aged 13, complaining of intense headache, vomiting, and stupor, and found to have marked double optic neuritis, with a swelling equal to 5 to 6 D. Four weeks previously he struck his head against that of another boy, and was slightly concussed. Headache supervened and persisted. In the course of three weeks he became drowsy and apathetic, and his parents noticed that he was becoming blind. It is to be remarked that before this accident the patient was an active schoolboy. He remained in this condition for a week, the knee-jerks disappeared, and nystagmus developed. Lumbar puncture brought away fluid under considerable pressure, apparently normal. He was trephined over the right temporal region by Cushing's method, and in three weeks he left the hospital practically well, with great diminution in the degree of the optic neuritis and impairment of vision. He was watched for some time, steadily improved, and remains well.

I submit that in a number of the cases which rapidly improve under decompression, especially posterior decompression, the pathological lesion may be effusion of fluid into the ventricles, without the presence of a tumour.

*3. Cases in which death occurs, the naked-eye appearances of the brain and meninges are normal, but microscopic examination has revealed a lesion.*

This group is becoming larger the more thoroughly the brain is examined.

Certain peculiar tumour formations may not be recognized unless great care is taken and disseminated lesions of encephalitis may escape observation.

Finkelnburg and Eschbaum have described in one case a peculiar chronic small-celled infiltration of the meninges at the base of the brain, invading the optic, olfactory, acoustic, and facial nerves, and the vessels of the medulla and pons; but the vessels did not show any signs of endarteritis, and the authors consider that the lesions they describe have no relationship to syphilis or tubercle. Mercury had no therapeutic effect.

The patient was a young man in previous good health; the duration of the illness was only eight weeks. He complained of pain in the head, giddiness and double optic neuritis were present, with paralysis of the right facial nerve, and deafness. To the naked eye no lesion of the brain was visible.

L. W. Weber and Schultz also record two careful microscopic examinations of the brain of persons dying with well-defined tumour-like symptoms. In one the naked-eye appearances were normal, in the other arterio-sclerosis of the basal vessels was seen.

Microscopical examinations in the first case discovered numerous cysts in the pia mater, forming an infiltrating tumour-like mass invading the brain stem, and in the second case there was extensive disease of the blood-vessels with infiltration in the vascular sheaths and oedema of the surrounding brain tissue.

*4. A few cases in which no lesion has been found even with a microscopic examination.*

Such was the case in the man Charles M., and it has been suggested as an explanation that a serous effusion may disappear before death. Nonne records three cases in which a microscopic examination failed to reveal any lesion. The symptoms were definitely those of increased intracranial pressure, in one case associated with epileptic fits, and in another with hemiplegia and abducens paralysis.

Lastly, reference may be made to Reichardt's observation, in conjunction with Reiger. These authors, from a long series of observations, state that the normal cranial capacity in cubic centimetres is 12 to 14 per cent. greater than the weight of the brain in grammes, and that this is very constant. Reichardt points out that it is notorious that neither the size, site of the tumour, nor its histological structure can sufficiently explain the cause of intracranial pressure; he believes that there is a pathological reaction of the brain, that a tumour forms a stimulus to the brain to increase in size and hence raise the intracranial pressure. This is different from hypertrophy of the brain described by some authors, which may depend on gliosis.

In the cases which Reiger describes, the chief objective sign at the post-mortem was osteoporosis of the skull and yielding at the sutures; there was a spreading out of the brain convolutions, tension of the dura mater, and a welling up of the brain after opening the skull, with signs of pressure against the foramen magnum.

Reichardt's measurements were taken after removal of the pia mater and choroid plexuses, and hence there was considerable loss of fluid, yet the pathological relationship between the skull capacity and the weight of the brain is found constant. Clinically, he regards optic neuritis, if diseased processes in the orbit, &c., can be excluded, as the most trustworthy sign of increased intracranial pressure.

Amongst his cases he relates one of a man aged 18, with a family history of insanity, and a personal history of 'fits' some years previously. He was admitted to hospital with melancholia on March 27, 1904; he had marked double optic neuritis, but no local signs of brain disease; there was no fever, and his appetite was good. On April 18 he was attacked with erysipelas, and died on the 22nd.

At the post-mortem examination the brain appeared normal; there was no



excess of fluid, and a minute histological examination revealed nothing beyond some hyperaemia and a new formation of capillaries; the volume of the cranial capacity was 1,400 c.c., and the brain weighed 1,510 grm., thus presenting a marked inversion of the ratio that he and Reiger have found so constant. The brain was quite dry and hard in consistence, and the swelling evidently preceded the attack of erysipelas.

Since histologically no specific tissue change was found, he suggests that there is an added albumin to the brain mass, brought in solution by the blood-vessels, and then re-precipitated in the nervous parenchyma, or in the minute spaces between the nervous tissue.

Had this case recovered, it would have been another example of a pseudo-tumour.

#### *Treatment.*

Little need be added to the indications given in the text. The subject is of much practical importance; it is cheering knowledge that a number of patients presenting symptoms simulating the gravest cerebral disease, may recover by natural processes or by the aid of simple procedures. The primary focus of infection, if it can be discovered, is to be at once removed. Then in the acute cases an attempt is to be made from the clinical evidence, and the examination of the cerebro-spinal fluid, to weigh the gravity of the disease. If any doubt, it seems best to act boldly by modern surgical methods. In the chronic forms, decompression of the brain is the treatment, though its success will depend on the duration and state of activity of the morbid process. In young children, on the whole, experience shows that conservative methods may be followed by the most fortunate results.

#### *Conclusions.*

1. The effusion may be the important pathological fact, and the prognosis and treatment depend upon a recognition of this.
2. The progress of an inflammatory effusion within the skull may be arrested at the serous stage.
3. The primary cause is commonly a near or distant focus of septic infection; the toxins formed by this, but not the micro-organisms, stimulate the vessels of the meninges, brain, or ependyma and choroid plexuses to the formation of excessive fluid.
4. The primary cause may also be toxins, generated by non-pyogenic organisms, and in rarer cases the excessive fluid results from causes other than toxins of microbic origin.
5. The symptoms in the acute or chronic condition respectively may simulate the gravest form of brain disease.
6. The diagnosis is suggested when there is reasonable evidence that the symptoms are those of increased intracranial pressure, if other well-known conditions can be excluded, and it is strengthened by the recognition of the primary cause.



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## EXPLANATION OF PLATE.

PLATE 8. R. T. (Case II, p. 109). Dilatation of the fourth ventricle and posterior part of iter.





# THE EXPERIMENTAL FORMATION OF ACUTE GASTRIC ULCERS

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With Plates 9-11

THE observations which are described in these pages developed in the course of some experiments made for another purpose. It has been known since Stern's work (7) in 1890 that tetrahydro- $\beta$ -naphthylamine, a fairly simple organic compound of the formula  $C_6H_4$   $\begin{array}{c} \text{CH}_2 \cdot \text{CH} \cdot \text{NH}_2 \\ | \\ \text{CH}_2 \cdot \text{CH}_2 \end{array}$  and not the isomeric body with

the  $\text{NH}_2$  in the aniline position, causes rise of temperature when injected subcutaneously into rabbits, and the drug has therefore been used by several workers for investigations into the physiology of fever (6). The adrenal glands play a considerable part in the reaction of fever; and in the wish to analyse their share in detail, I examined the reaction of the glands to injection of this drug.

My first experiments were made on cats (3). It was found that the injection caused rapid exhaustion of adrenalin from the glands, and that the loss was effected indirectly by nervous impulses playing on the glands through the splanchnic nerves. Marked rise of temperature, however, did not occur in these animals. Instead, the drug caused a persistent state of psychic alarm and anger; and it seemed that the consequent nervous exhaustion of adrenalin from the glands was to be explained by this emotional effect. Guinea-pigs were next employed. Slight alarm and fever with adrenalin exhaustion resulted; but in this animal a fresh phenomenon was seen, the appearance of acute ulcers in the stomach. These developed with such certainty and rapidity that a series of observations was made upon them alone, partly because the reaction illustrated well one of the ways in which an acute gastric ulcer may be caused, and partly in the chance hope that it might be capable of repetition, so as to produce a chronic gastric ulcer, a hope that was not realized. The results of the experiments were as follows.

The drug tetrahydro- $\beta$ -naphthylamine hydrochloride, which in the rest of this paper is for brevity called  $\beta$ -tetra, was dissolved by heat to a 1 per cent.

<sup>1</sup> Working in tenure of a Beit Memorial Fellowship, and aided by a grant from the Graham Research Fund, University College Hospital, London University.

solution in neutral Ringer's fluid or in normal saline. On cooling, a yellow solution was obtained, which slowly darkened with keeping, while a brown precipitate appeared in the course of a few days. A fresh solution was generally employed. This was injected subcutaneously over the abdomen. No signs of pain at the site of injection were caused, but in ten minutes or so the general toxic effects appeared like those in the cat. The hairs were raised over the shoulders and down the back, and the eyes were widely dilated, while the animal became very restless and shook its head up and down. Later, irregular convulsive movements appeared in the body and limbs, and the hind legs were partly paralysed. There was no evidence of asphyxia by constriction of the bronchioles. If the dose of the drug were excessive, the phenomena of paralysis increased, so that the animal lay feebly on its side with the legs twitching weakly, and death followed in a few hours. This fatal result might occur with 2 to 4 c.c. of 1 per cent.  $\beta$ -tetra.

With an appropriate injection the phenomena of excitement and poisoning passed away in a few hours, and the guinea-pig became to all outward seeming perfectly normal again. It ate its food eagerly, and ran about the cage without any token of gastric discomfort. None the less, acute ulcers were then always found to be present in the stomach, if the animal were suddenly killed.

#### *Course of the Ulcers.*

The ulcers developed with great rapidity. The guinea-pigs were killed by a sudden blow on the head, which was then cut off. Under these conditions the heart continued to beat vigorously, and the vessels were more or less emptied of circulating blood. Asphyxial haemorrhages were avoided, and the distension of a vein or capillary with blood could justly be ascribed to local damage of the circulation caused by the poison before death.

*One to two hours* after the injection, ulceration was always visible in the stomach. Externally, this could be recognized by purple-coloured patches of congestion seen through the peritoneal coat. Within, the damaged area looked much as a stomach does when a corrosive acid has been swallowed, an irregular swollen patch of haemorrhage and erosion being surrounded by a wide margin of a greyish colour without haemorrhage. These changes always occurred in the stomach. Very occasionally small haemorrhagic areas were also visible in the mucous membrane of the colon, caecum, and duodenum. These were caused by extravasation of blood from congested small venules; but the cells of the overlying mucous membrane seemed to be normal. One may dismiss these haemorrhages from subsequent description by saying that the blood was soon absorbed as the circulation improved; the mucous membrane remained intact, and ulcers never developed in either colon or duodenum.

In the stomach it was otherwise. The same circulatory congestion was observed with dilatation of the capillaries in the mucous membrane, though no thrombosis could be detected in the larger vessels of the submucosa. But the



cells of the mucous membrane were also changed, and this change generally spread over a far wider area than that of the haemorrhages. To the naked eye it was visible as a greyish white membranous pellicle. Under the microscope<sup>2</sup> the columnar epithelial cells in the affected area were all found to be altered. Their nuclei stained ill, purple or pink instead of blue with haematoxylin and eosin, and were often vacuolated. Masses of these dying cells were breaking away to form the grey pellicle already described. Deep down, and close to the submucosa, the cells were quite normal and healthy. Between them and the devitalized surface was a zone of varying depth in which the gastric tubules also were breaking up. Loosened from their bed, the individual cells pressed up to join the debris of necrosed cells on the surface. The oxyntic (parietal) cells floated freely in this exudate, and by their bright pink stain with eosin seemed even to be alive. A few clumps of red corpuscles were seen where a capillary vessel had been laid open, and projecting into the debris were the bare branches of connective tissue upon which the gastric tubules had been built up (Figs. 6 and 7).

No deeply situated foci of destruction were ever observed. The appearances were simply those of a necrosis and erosion spreading downwards from the surface, first through the protecting sheet of epithelial 'mucous' cells, and then rapidly down the framework of the tubules. The cells seemed to be loosened from their basement membrane by the action of the invading gastric juice before they were actually killed and digested. In one hour after the injection the necrosis may have extended down through the entire depth of the mucous membrane.

*Twenty-four hours.* The guinea-pig had now recovered completely, and ate with alacrity. Its stomach showed irregular wide areas of obvious ulceration, red, excavated, with oedematous overhanging edges. Such ulcerated areas were present chiefly over the fundus and greater curvature, and they were never seen in the close neighbourhood of the pylorus.

Microscopically, the necrosis reached down to, but did not affect, the muscularis mucosae; and, to a slight extent, it spread laterally at the base so as to undercut the overhanging oedematous mucous membrane around it. Most of the necrosed tissue was already separated and swept away.

*Three days.* The ulcers were very obvious to the naked eye, and they were either infected or clean. The former had a greenish yellow slough on its surface, whereas the latter was red, smooth, and glistening. Healing was extremely rapid. A *clean ulcer* of two centimetres in diameter might in three days be completely covered by a surface pellicle of repair cells. The microscopic appearances of such a clean healing ulcer are as follows: In the submucosa below there is

<sup>2</sup> The stomach wall was washed lightly with warm Ringer's solution, but not brushed clean. It was then pinned out in the fixing solution. A mixture of formalin, mercuric chloride, and glacial acetic acid gave perfect fixation, but the staining after it was always dull and poor in contrast. Best was formalin and salt, followed by slow dehydration. The tissue was cut in paraffin. Sections were also cut frozen by the gelatin method and stained for fat, but neither this nor the mucicarmine stain gave any further information with regard to the nature of the ulcerative process.

a slight thickening due to enlargement of the local fibroplastic connective-tissue cells, and there is a very slight round-celled exudation. Above the muscularis mucosae lie the dead gastric tubules, now an amorphous mass between which pass dilated capillaries from which blood has extravasated here and there. Shielding this from the action of the gastric juice is a thin layer of new epithelium, formed of cells which are cubical or flat, and at first do not overlies one another. At the edge of the ulcer these pass up into the columnar cells of the normal epithelium, but they do not seem to have been all derived by an outgrowth of the latter over the bare area. Indeed, the layer is often very thin or incomplete near the edge, while it shows irregular thickenings in the centre of the ulcer, and separate islets of it may be seen with rounded edges of such a character that they could not have been isolated by tearing in the process of histological preparation (Fig. 10).

This repair epithelium seems to be derived directly from cells that pass up to the surface with the irregular blood-vessels. Where it occurs in thickened masses, there is generally to be seen below the debris a clump of live cells belonging to the deep extremity of the gastric tubules which has survived the destruction of the upper end. These in all probability supply the repair cells of the surface, upon which the separate islets grow rapidly and fuse to a complete sheet which can resist the gastric juice, despite its fragile nature. It is only in unfavourable cases, where the surface is septic and the tubules have been destroyed right down to the muscularis mucosae, that the repair epithelium must grow inwards from the edge of the ulcer, and so the whole sheltering process be delayed. Griffini and Vassale, twenty-five years ago (5), described very clearly the development of this covering layer in dogs, from which they had cut away small sheets of the gastric mucous membrane; and they argued that it was derived from the glandular cells of the gastric tubules at the edge of the wounded area, and not from the surface epithelium. In their dogs it took five or six days to develop; and later, by reason of its glandular derivation, it was able to form gastric tubules and restore the functions of the mucous membrane.

When the ulcer has become *septic* by a secondary infection, the histological picture is altered by the reactive inflammation. The vessels of the submucosa are engorged, and the areolar tissue around them is laden with round cells and polymorphonuclear leucocytes. Polymorphs stream through the debris of the gastric tubules and appear with effused blood on the surface slough. A repair epithelium can be detected in patches, but its growth is seriously checked by the slough. The microphotographs (Figs. 10 and 11) illustrate a septic and a clean ulcer, which were both found in the stomach of the same pig three days after the injection of  $\beta$ -tetra.

*Subsequent history.* The later progress of the ulcer calls for no special comment, because it follows closely the descriptions given by pathologists who have used other methods to bring about the change. If the ulcer remains infected, the muscularis mucosae may be destroyed, and the ulceration extends deeper. Actual perforation into the peritoneal cavity never occurred in my

guinea-pigs, because the omentum always became adherent to the stomach when the inflammation reached the peritoneal surface, and these adhesions sealed off the damaged part. At this time the gastric tubules of the non-ulcerated mucous membrane in the immediate neighbourhood of the ulcer become cystic, apparently by dilatation from blockage of their outlets. The fluid in these dilated tubules does not digest the surrounding cells, but it frequently contains polymorphs floating within it.

Haemorrhage into the cavity of the stomach was occasionally observed in the early stages of an ulcer formation, when it was due to a general extravasation from the wide area of ulceration. In the later stages no large vessel was ever opened, and death never occurred from haemorrhage.

Twenty days was the latest date at which the injured stomach was examined. No puckering or adhesions were seen in simple non-septic cases, but the areas over which ulceration had occurred were visible through the thin stomach wall as opaque patches. Microscopic sections showed a fully regenerated columnar epithelium covering a mucous membrane, which was of about half the normal depth, and contained tubular glands that were still characterized by their irregular cystic dilatation.

*Repeated injections of  $\beta$ -tetra* were given in a few cases. Each fresh injection was followed by the formation of some fresh ulcers, and the old ulcers remained septic, so that they extended through the muscularis mucosae, and even to the peritoneal coat. Apart from the spreading effects of such sepsis, there was no tendency noticed for the ulcers to remain and pass into a chronic state. Consequently, the experiments were not carried any further.

As stated earlier in this paper, the drug may kill the guinea-pig in the first few hours by a general toxic action altogether apart from its effect on the stomach. When the injections were repeated, the animals certainly became more tolerant of the poison.

In the female the drug tended to cause haemorrhage in the uterus, and occasionally this resulted in abortion when the animal was pregnant. In two cases abortion did not result, and while ulcers were found in the mother when she was killed, there were none in the stomachs of her foetus, the gastric contents of the latter being neutral.

#### *The Cause of the Ulcers.*

The rapidity with which these ulcers are formed, before septic infections have time to confuse the process, is an advantage for their study. Under the microscope, it is clear that the necrotic process commences in the surface epithelium. The columnar cells of the latter are not mucilaginous in the guinea-pig,<sup>3</sup> but they serve to protect the underlying gastric cells from the action of the juice

<sup>3</sup> Indeed, very little mucus is secreted in the guinea-pig's stomach, and the mucicarmine stain reveals mucus only in the special cells at the bottom of the gastric tubules close to the pylorus, cells which enlarge to form the Brunner's glands of the duodenum, whence mucus is poured up between the crypts.

in the stomach. The injected drug is absorbed into the circulation, and in view of the haemorrhages that may occur elsewhere, there is no reason to believe that it is excreted especially into the stomach. But its presence in the body-fluids lessens the vitality of the gastric mucous membrane to such a degree that the latter is at once digested by the gastric juice. Similar devitalizing changes are caused in the duodenum and lower down the alimentary canal, but here ulcers never result, because there is no gastric juice to assail the mucous membrane in its time of distress. Indeed, the comparative harmlessness of the drug itself is proved by the fact that the subcutaneous tissues at the site of injection never slough nor show destructive changes.

The juice is elaborated within the gastric tubules, and it is conceivable that the actual necrosis might in consequence start within them at the point where the juice is supposed (4) to be liberated with fully-developed peptic powers. As a matter of fact, however, the necrosis begins always at the surface, and does not spread downwards between the tubules until the outer epithelium has been denuded. Clearly it is caused by the eroding action of the gastric juice then present in the stomach, and consequently the histological picture in the first hour of ulceration is like that seen in post-mortem digestion of the gastric mucous membrane.

This deduction from the microscopic features was confirmed by experiment. Pairs of guinea-pigs were injected with similar amounts of  $\beta$ -tetra. One in each pair was fed before and after injection; the stomach of the other was kept as nearly empty as possible by abstinence from food and drink. Next day both were fed equally, and two days later both were killed. In every case the fed animal had extensive ulceration, while, with two slight exceptions, the starved pig showed no ulcers at all.

It is obvious that these experiments reinforce the views of Bolton (2) upon the formation of acute gastric ulcers. Bolton states that 'an acute ulcer is produced by gastric juice acting upon a damaged portion of the mucous membrane, the damage being caused by either localized necrosis, or an interstitial haemorrhage, or inflammation of the lymphoid follicles'. His experiments were made with a specific gastrot toxin contained in an immune serum, which was injected into the peritoneal cavity of guinea-pigs. The serum was absorbed into the blood-stream and produced multiple patches of necrosis in the mucous membrane of the stomach, with ulcers a few hours later. He proved that such ulceration was invariably prevented by the previous introduction of a weak alkali into the stomach so as to neutralize the gastric juice. He also found that, by injecting the serum directly into the wall of the cat's stomach after the abdomen had been opened, an ulcer was formed in three days. This was fully healed again in twenty-one days, unless unhealthy conditions in the base of the ulcer, due to septic necrosis or deficient blood supply, delayed the overgrowth of the epithelial cells. The ulcer failed to appear if the cat's stomach was kept empty by starvation (1, p. 236). These experimental facts were used by him to emphasize the frequency with which acute gastric ulcers may form and heal in the human

stomach, giving rise to practically no symptoms except in the dramatic crises of haemorrhage or perforation, or when sepsis and other unfavourable circumstances convert them into a chronic, open sore.

$\beta$ -tetra provides the analogy with the type of *acute gastric ulcer in man that may break out in a quite healthy stomach* as the result of processes elsewhere in the body that are leading to the formation of toxic substances, such as the infectious fevers, sepsis from a wound, and so on. These ulcers in man form quickly; provided there is no septic infection of their surfaces, they heal with equal rapidity. And in the vast majority of clinical cases they pass unnoticed, except when they chance to be associated with haemorrhage. So it is with the guinea-pig's stomach and this drug. Injected anywhere beneath the skin, it is absorbed and poisons the vitality of the gastric cells to such a degree that they can be digested by the gastric juice if there is any of the latter free within the stomach. Moreover, since the ulcer is completely formed within an hour or two after the injection, it is obvious that the process must be entirely apart from bacterial infection.

Various writers since the time of Virchow have supported theories which emphasize the development of acute gastric ulcers as the result of mechanical changes in the circulation, minute emboli or vascular spasm hindering the blood-flow, and so by anaemia devitalizing the cells. That is not probable with  $\beta$ -tetra. It does not cause rise of blood-pressure nor spasm of the larger vessels, and the devitalizing process is too rapid. Capillary haemorrhages are numerous with it, but their appearance suggests a toxic rather than an embolic cause. Moreover, the first change seen in the area that is to become ulcerated is often the appearance of a white membranous film, due to epithelial change, and beneath this there may be no haemorrhage at all, and only capillary stasis. Still, it cannot be said with certainty that the gastric cells are affected primarily by the toxic drug, and that they are not devitalized as the result of damage to the capillary circulation.

In other animals, namely the cat and the rabbit, actual ulceration is not caused by this drug, whether injected beneath the skin or directly into the gastric wall, so that it cannot be used generally for the study of gastric ulcers.

#### *Summary.*

The substance tetrahydro- $\beta$ -naphthylamine hydrochloride, when injected subcutaneously in guinea-pigs, causes the formation of acute gastric ulcers. These result from the action of the gastric juice on the damaged mucous membrane, and they do not appear if the stomach is kept empty of food. The ulcers form in one or two hours, and they heal with great rapidity, unless they chance to become septic. Repair epithelium covers the raw surface within three days, and from this the glands are regenerated later.

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## DESCRIPTION OF FIGURES.

PLATE 9, FIG. 1. Haemorrhagic ulceration of stomach. Well-fed guinea-pig: killed 2½ days after the injection of 3 c.c. 1 per cent.  $\beta$ -tetra. There are several clean ulcers in the main area, but sepsis is present here and there, and the intervening areas of mucous membrane show haemorrhagic changes.

A second guinea-pig, which received the same injection under similar conditions, showed simply one large, clean ulcer; and a control animal, which was starved before and after the same dose, showed no ulceration at all.

FIG. 2. Perforated ulcer. Two smaller ulcers are visible above. Injections of 2.5 c.c. and 3 c.c. at 9 and 2 days before death.

FIG. 3. Slightly septic ulcers. Between the lower large and the upper small ulcer is a whitish area of partial necrosis that has not ulcerated. No blood in stomach: no ulcers in bowels. Caused by repeated injections of 1.5, 2.5, 3, and 4 c.c. at 25, 18, 11, and 2 days before the guinea-pig was killed.

FIG. 4. Three septic ulcers with sloughs, the two lower ones being on the point of perforation. Two minute clean ulcers are also present, but they are not conspicuous in the photograph. Caused by successive injections of 3, 2, and 2 c.c. at 18, 9, and 2 days before the animal was killed. Two small haemorrhagic areas were present in the colon, but no ulcers anywhere except in the stomach.

*Micro-photographs.* The sections of the guinea-pigs' stomachs are lettered throughout as follows:

- c.e.*, columnar epithelium of surface.
- r.e.*, repair epithelium of surface.
- g.t.*, gastric tubule.
- eos.*, eosinophil (oxyntic) cell of tubule.
- bl.*, blood corpuscles.
- m.m.*, muscularis mucosae.
- e.m.*, external muscular coat.

PLATE 10, FIG. 5. First stage of ulcer formation: killed ½ hour after injection of 2 c.c. 1 per cent.  $\beta$ -tetra. On the right the mucous membrane is normal, but to the left it is breaking away from the surface above the gastric tubules. There are no capillary haemorrhages. Much deeper ulcers were present elsewhere in the same stomach.

FIG. 6. 2½ hours after injection. The tissues of the submucosa and the two large vessels in the subserous coat are normal. Two thrombosed veins (*t.v.*), of darker tint, are seen in the base of the mucous membrane, which is largely destroyed. From the upper half of the mucous membrane the cells have gone, and only the connective-tissue framework is left. Above this the field of the micro-photograph is occupied by a mass of debris of effused blood and cells of the gastric tubules. In the upper part of this debris the extruded cells are disintegrated, but lower down they have retained their shape and staining qualities so that the eosinophil cells are easily recognized.

FIG. 7. Higher magnification of part of Fig. 6, showing the disintegrated tubules below, and above these the debris formed by escaped cells in a mass of blood corpuscles.

PLATE 11, FIG. 8. Ulcer at 24 hours reaching down to the muscularis mucosae, beneath which is a slight accumulation of round cells. The gastric tubules are entirely necrosed, but have not been removed. At the edge the intact mucous membrane overhangs the tiny ulcer, and its tubules are separated from one another by oedematous exudate (*ex.*).

FIG. 9. Clean healing ulcer, 3 days. On the left, intact mucous membrane with cystic dilatation of its tubules. Over the ulcer the tubules have completely gone, and the floor is covered by a flat layer of repair epithelium 3 or 4 cells thick. Below this the muscularis mucosae is intact except at the right of the field. There is no inflammation.

FIG. 10. Clean, healed ulcer, 3 days. Necrosis extended down to the base of the mucous membrane, but the dead tissue has not been removed. It is covered by a repair epithelium, which is one cell thick at the right edge, where it passes into the columnar epithelium of the mucous membrane, but at X is heaped up into a mass several cells deep. No inflammation in the submucosa.

FIG. 11. Septic ulcer, 3 days. Mucous membrane and muscularis mucosae are both destroyed; there is no repair epithelium, and the whole field is occupied by a crowd of polymorphonuclear leucocytes and effused blood corpuscles. There was much perivascular inflammation in the large vessels outside the area photographed. Figs. 10 and 11 are different ulcers from the same stomach.



FIG. 1

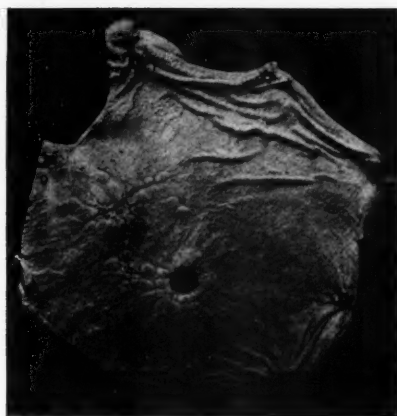


FIG. 2



FIG. 3



FIG. 4



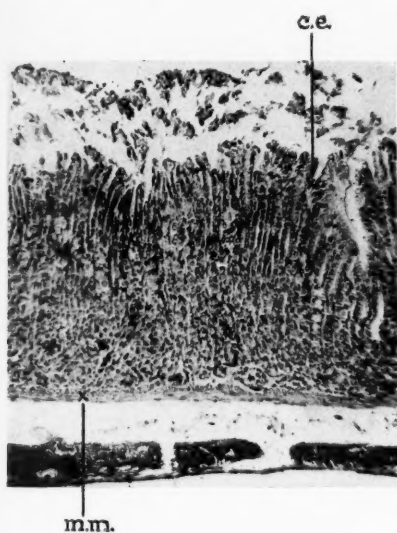


FIG. 5

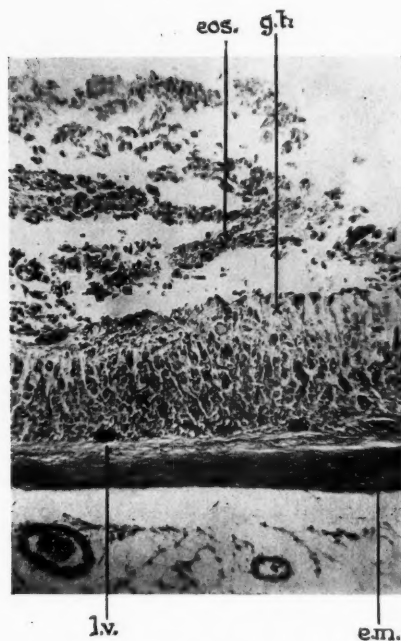


FIG. 6

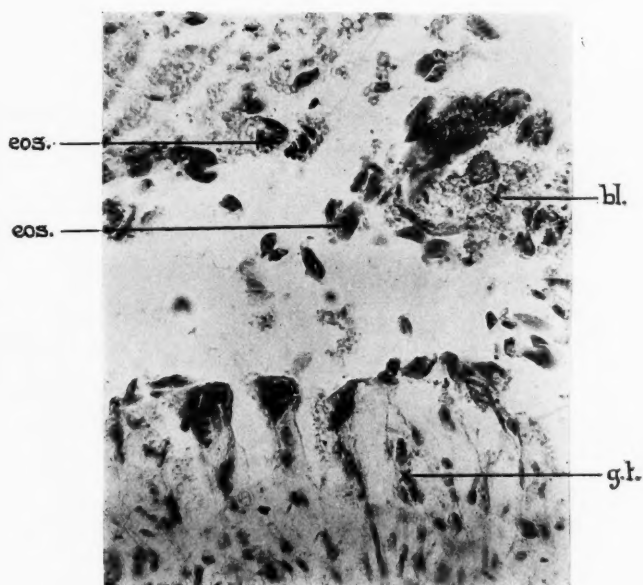


FIG. 7





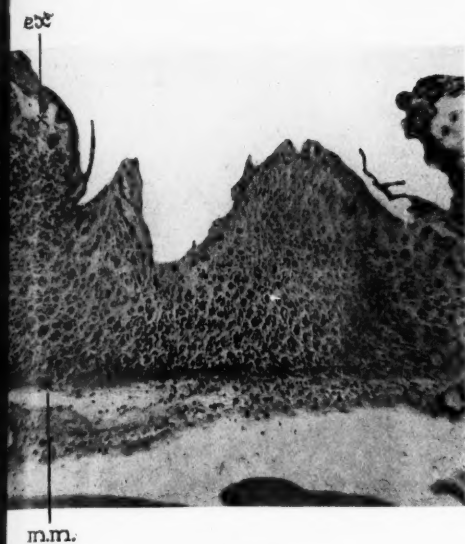


FIG. 8

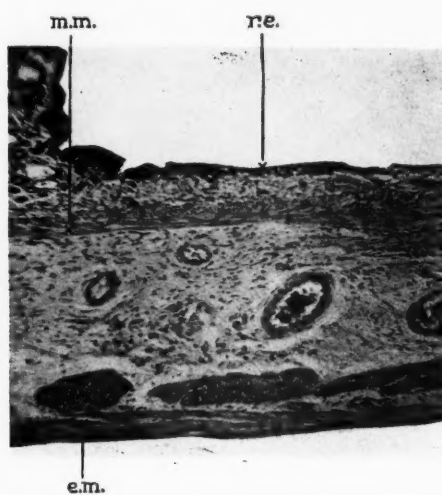


FIG. 9

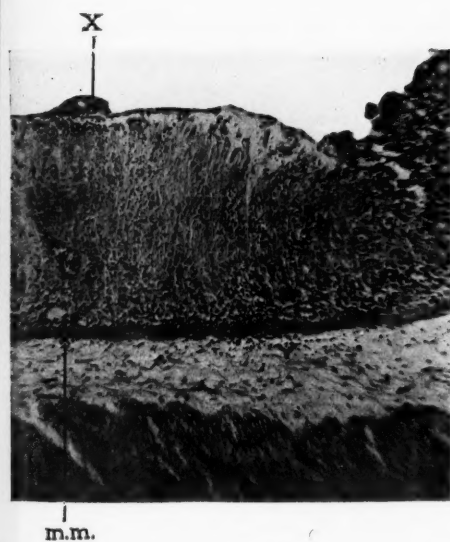


FIG. 10

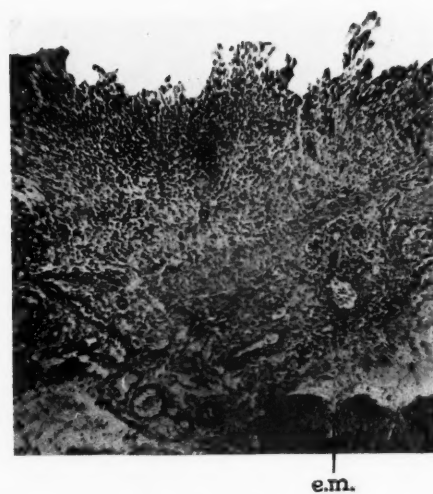
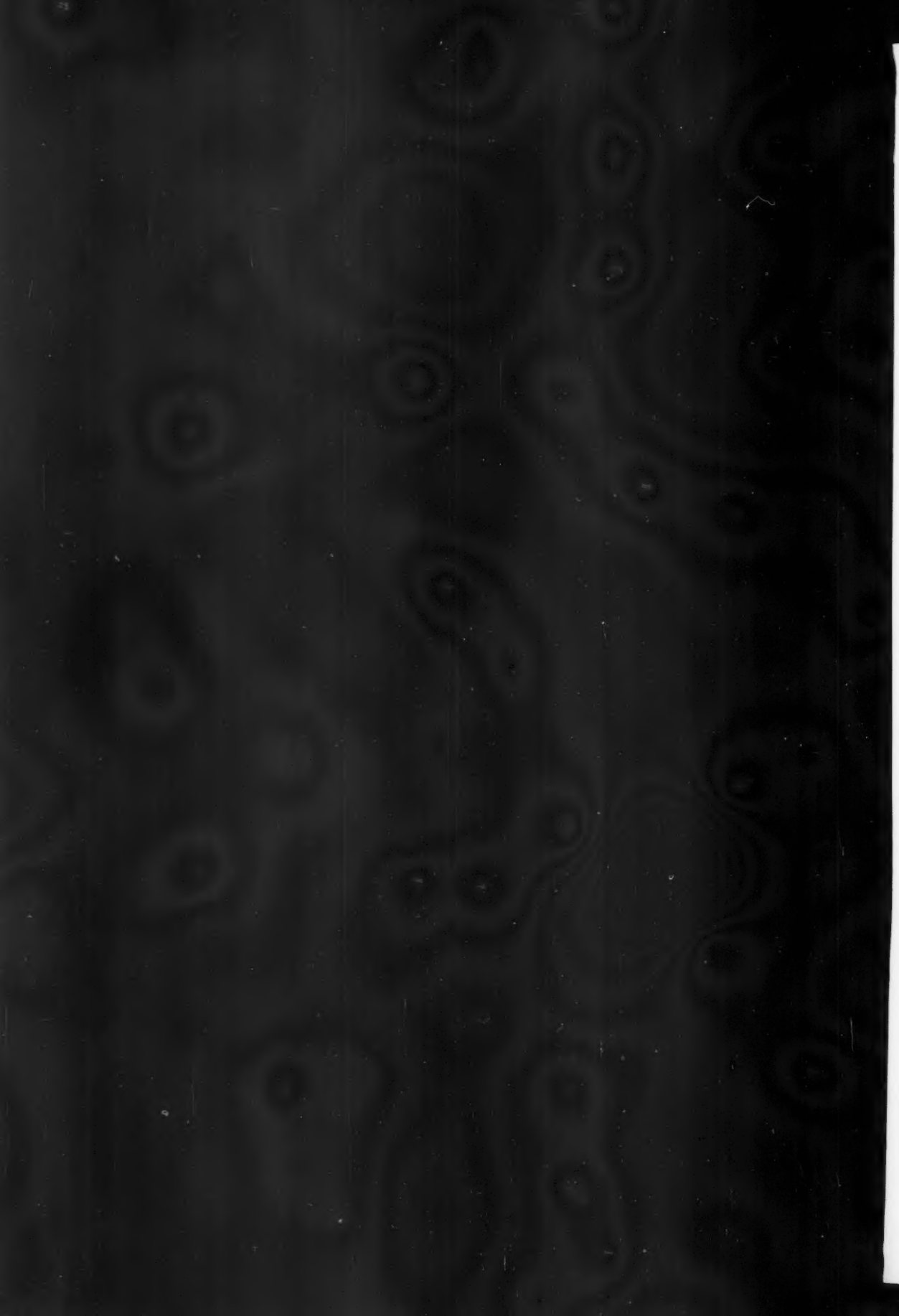


FIG. 11



## A CONTRIBUTION TO THE STUDY OF BRONZED DIABETES

By

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With Plates 12-14

*Introductory Remarks.* (A. E. G.)

THE syndrome which is commonly spoken of as bronzed diabetes, and which is characterized by the association together of cirrhosis of the liver, the peculiar pigmentation of the skin and viscera known as haemochromatosis, fibrosis of the pancreas, and, as a rule, persistent glycosuria, has been observed so often that one can hardly doubt that in it we are confronted with a pathological entity, and with no mere accidental grouping of morbid events. Nevertheless, we are still far from any adequate understanding of the condition; and the wide differences of opinion which exist as to the sequence of the events and the relative importance of the several factors bear witness to the need for further investigations and studies of individual cases.

The present paper embodies the outcome of the study, by a group of workers, of a very characteristic case of bronzed diabetes which was recently under observation in my wards in St. Bartholomew's Hospital.

Having been asked to edit the results of the work, I have thought it best to leave the several contributors to tell their own story, the share of each being indicated by his initials.

Although this plan detracts somewhat from the continuity of the whole, seeing that the views expressed in the various sections are not always in accord, it has the advantage of allowing expression of individual opinions based upon different lines of investigation.

A. F. Sladden and R. L. Mackenzie Wallis contribute the sketch of the present state of our knowledge of the subject, the account of the clinical features of the case and of the examinations of the blood, ascitic fluid, and excreta, and the results of tests of pancreatic efficiency. The latter also discusses the iron meta-

bolism of the patient. J. F. Gaskell and P. T. Vaile contribute the account of the histological examination of the organs and tissues.

We would express our sincere thanks to others who have helped us in various ways, to Dr. Adamson for his report upon the skin, to Dr. Thursfield for his notes of the post-mortem examination, and to Dr. Cammidge for his independent examination of the urine and faeces.

*Historical Sketch.* (A. F. S. and R. L. M. W.)

The history of the study of bronzed diabetes reflects in an interesting manner the changing opinions as to the pathogenesis of the condition.

A very complete account was given by Anschutz in his paper of 1899, whilst more recently T. P. Sprunt has reviewed the whole subject at considerable length, showing the development of theories advanced to explain the aetiology of the disease. A short summary may help readers to grasp the essential features of the disease, and at the same time will avoid an unnecessarily detailed exposition of the subject, the history of which has been so fully given by recent authors.

The earlier French observers, Hanot and Chauffard, regarded the glycosuria as the main feature of the disease, and drew attention to the pigmentation as a secondary phenomenon.

Hanot and his collaborators described the more important histological changes accompanying the disease, and although their conclusions as to the genesis of these changes are not now accepted, their observations remain as the first detailed account of the pathological appearances found in the disease.

A new light was thrown on the subject in 1889 by von Recklinghausen, who described a condition of pigmentary cirrhosis of the liver and pancreas, not accompanied by diabetes. He applied the name haemochromatosis to the condition, and described two pigments found, one 'iron-containing' haemosiderin, and the other 'iron-free' haemofuscin. This distinction, based on the reaction of the pigment to hydrochloric acid and potassium ferrocyanide, has since been maintained rather rigidly, with no great advantage.

The association of pancreatic disease with glycosuria, shown by v. Mering and Minkowski's work in 1890, led naturally enough to some reconsideration of the relative importance of glycosuria in the condition of bronzed diabetes, and Buss suggested in 1894 that haemochromatosis, of exact cause unknown, was the precursor of diabetes in these cases.

Speculation now centred more particularly around the origin of haemochromatosis, and a primary blood disease was postulated as first cause, involving a break-down of haemoglobin, subsequent deposit of iron-containing pigment in the glands, and later, by the irritative action of the pigment, a sclerosis of the gland tissue.

This view was in the main upheld by Anschutz in his summary of 1899, but

he noted a weak point in the theory, namely, the absence of evidence of any great blood destruction, which hypothetically must take place.

A most important contribution following Anschutz is that of Opie, who laid stress on the significance of the pigment deposit being most dense in those sites where physiologically there is some pigment; in other words, he indicated the possibility of the pigment formation being a normal process running riot.

Most authors at this period (1900-1) held that a common cause underlay the pigmentary changes, the cirrhosis, and the diabetes, and that these three main features were independent of each other, but all dependent on a primary cause. But it was also generally admitted that there might be an auxiliary action, in the case of the cirrhotic pancreas, tending to increase the glycosuria.

A fresh idea was put forward in 1903 by Parker, who suggested that the increase of iron in the tissues was due to defective iron excretion rather than excessive blood destruction, and there is much to commend this view. In no case is there satisfactory evidence of great blood destruction, whereas there is evidence of diminution of iron excretion, e.g. in our case no iron at all could be detected in the bile and faeces, and the percentage of iron in the blood was appreciably above normal.

The nature and origin of the pigments found has of late occupied much attention. The hard and fast division of pigments into haemosiderin and haemofuscin is not so well founded as to evade criticism. Abbott in 1901 showed that some 'haemofuscin' pigments, if treated with hot hydrochloric acid, would give an iron reaction; others, however, e.g. the granules in muscle cells, would not react thus. It is probably a question of the mode of combination of the iron, whether ionized or not, rather than the presence or absence of the metal in the pigment, which determines the Perl reaction.

The causation of the cirrhotic changes observed still requires an adequate exposition, and the possibility of a parenchymatous degeneration taking place, as part of a general disturbance of metabolic processes, is being discussed at the present time.

Such cellular break-down may at any rate contribute towards the establishment of fibrous tissue within the glands, even if it does not afford a complete explanation.

Simultaneously—in fact, as a part of the degenerative change—would proceed the deposition of pigment, and naturally subsequent histological examination would show a close association between pigment granules and fibrous tissue. Potter and Milne do not think that the deposition of pigment causes inflammatory changes in the glands; in fact, they found the parenchymatous cells least degenerated where there was most pigment, a condition which does not accord with either of the afore-mentioned theories.

These authors believe the cirrhosis of the liver to be the primary cause of the disease, and pancreatic cirrhosis, sequent or coincident, to determine the presence of glycosuria. They point out that all cases of hepatic cirrhosis are accom-

panied by some degree of pigmentation, and regard haemochromatosis as merely an extreme form of such pigmentary deposition.

As a consequence of the views here narrated, the possibility of the pigment having its origin in tissue protoplasm, rather than from blood pigment, has recently been mooted, and Sprunt supports this view.

The knowledge that pigmented substances can be formed from proteins by way of the tyrosin fraction has been established in the case of alkaptonuria, and an analogous process may explain the deposition of iron-free pigments in bronzed diabetes.

The subject is rapidly resolving itself into a problem in metabolism for the pathological chemist, and it is on chemical lines that further advance is to be anticipated.

It is seen then that the diabetes, the haemochromatosis, and the hepatic cirrhosis have all in turn been regarded as the underlying cause of the disease, but in no case has the theory received complete proof, and it certainly appears necessary to search further back for a primary condition which leads to all three manifestations.

Incidentally this should advance very much our knowledge of the pathogenesis of cirrhosis and of diabetes, so that the study of bronzed diabetes, a condition very rarely seen, has an important bearing on diseases of common occurrence, and has a significance far beyond that of a mere pathological curiosity.

Whatever be the exact underlying cause of the disease, there appears to be full justification for regarding bronzed diabetes as a clinical entity, even though it prove to have in its aetiology much in common with haemochromatosis.

At least sixty cases of bronzed diabetes are on record, also a number of haemochromatosis without diabetes, and some cases of doubtful nature. As the cases of bronzed diabetes have so recently been tabulated by Potter and Milne, we will content ourselves with referring to a few recorded since they wrote, viz. those of Chaliér and Nové-Josserand, Labbé and Bith, Vanderhoof and Hutchinson, A. Gouget and Rosenberger, which are included in the list of references at the end of our paper.

*Clinical History of the Case studied.* (A. F. S. and R. L. M. W.)

Peter B., aged 44 years, a pharmaceutical chemist, was admitted to Colston Ward, St. Bartholomew's Hospital, on April 17, 1912, suffering from diabetes. About the previous December he was first noticed by his wife to eat and drink more freely than usual, and she also noticed an odour similar to that which she had observed in the case of her father, who had died of diabetes. In January, 1912, the patient tested his own urine and found it to contain sugar. Between December and April he had lost 18 pounds in weight.

Both his parents were alive, and no history was obtained of diabetes or abnormal pigmentation in any member of his family. The patient said that he had suffered from psoriasis for thirty years. He denied syphilis, but admitted that he had taken 'a fair amount' of alcohol in earlier life. No date could be obtained for the commencement of pigmentation of his skin.

Condition on admission: The patient was a lean man with a peculiar



dusky complexion. He was somnolent and apathetic, and usually lay with his eyes closed. His likeness to an Egyptian mummy struck several observers. The appearance of his skin was thus described by Dr. Adamson:

'The skin of the face is of a uniformly dark-bronze colour, save that over the temples and adjacent parts the bronzing is much darker than on the rest of the face.

'The trunk and limbs present a generalized mottled pigmentation. The skin appears to be covered with deep reddish-brown, somewhat scaly patches of the size of a finger-nail, and these are specially pronounced upon the sides of the abdomen and upon the limbs. On closer inspection it is seen that the dark patches are connected up by bands of a paler and somewhat redder colour, so that the whole effect is that of a pigmentary network with paler meshes—*melanoderma reticulatum*. The reticular distribution of the pigment resembles the dusky network seen in *livedo annularis*, and the distribution of the stain seen in pigmentation from prolonged exposure of the skin to heat. It is doubtless dependent upon the anatomical arrangement of the blood-vessels of the skin, and indicates that the pigment has been deposited in the areas of vascular congestion or reduced circulation.'

No pigment was to be seen on the tongue or buccal mucous membrane. *Venae stellatae* were present in the skin of the face.

The teeth were few and in bad condition; the gums were spongy and bled readily. The tongue was the characteristic red and beefy tongue of a diabetic. The chest did not move well on respiration, and was very poorly covered. The air entry was poor and a few moist râles were heard over the lungs. The area of cardiac dullness overlapped the sternum to the right, but no other abnormality was found in the heart.

In the abdomen a prominent mass was seen in the epigastric region, extending towards the left. This was found to be continuous with the liver and moved with it on respiration, and the right lobe of the liver was palpable below the costal margin. The greatly enlarged left lobe was hard and was not tender. The spleen was not felt.

The urine was found to contain glucose and diacetic acid. On the day of admission its specific gravity was 1.030.

The course of the disease was steadily progressive. The patient was at all times lethargic and apathetic, as if upon the verge of diabetic coma. He was given a mixed diet with reduced carbohydrate content. On April 22 small purpuric spots appeared upon the abdomen, and a week later a red macular eruption was observed over the same area. The abdomen became fuller, partly from tympanites, partly from commencing ascites, and there was some congestion at the base of the left lung.

During May the apathy and drowsiness increased, as also did the ascites, and general anasarca developed. On May 2 the urine had ceased to yield Gerhardt's iron reaction, and twelve days later Rothera's reaction also was no longer obtained. Owing to increasing ascites paracentesis was called for, and on May 20 nineteen and a half pints of ascitic fluid were drawn off. This fluid contained 0.186 per cent. dextrose, 20.5 grammes in all. After the paracentesis the liver was found to be larger than it had been at the time of admission. By the end of May signs of cystitis had appeared, the fluid reaccumulated in the abdomen, and there was increasing pulmonary oedema.

During June there was a marked increase of the bronzing of the skin, the patient's condition became steadily worse, and on June 17 he died.

*Examinations of the urine.* Daily estimations of the sugar in the urine were carried out. From April 21 to May 23 the average daily total was 113 grammes, the extreme limits being 178.2 and 60.4 grammes respectively. After the appearance of pus in the urine on May 29 the percentage of sugar tended to diminish, possibly as a result of the multiplication of bacteria in the

urinary tract. The disappearance of the iron reaction of aceto-acetic acid from May 1 and of the more delicate Rothera's reaction from May 13 has already been mentioned. There was no conspicuous polyuria at any time whilst the patient was in the hospital.

The results of examinations of the urine on certain dates may be given as samples.

Urine of April 22: Total quantity excreted in twenty-four hours, 2,400 c.c. Sp. gr. 1,036. Reaction alkaline, no albumin. Total sugar, 152 grammes (6.3 per cent.). Diacetic acid present. No urobilin, no indican.

The Cammidge test, carried out against a control, was wholly negative in duplicate tests made independently by the writers, and a specimen of the urine of May 31, which Dr. Cammidge himself was kind enough to examine, yielded no 'pancreatic reaction'.

Urine of May 1: Total quantity, 2,700 c.c. Sp. gr. 1,038. Acid. Degree of acidity, 13.6 per cent.

Total nitrogen	. . .	0.605 per cent.	=	16.33 grammes in 24 hours
Urea	. . .	1.4	"	= 37.8 " "
Creatinine	. . .	0.026	"	= 0.7 " "
Ammonia	. . .	0.031	"	= 0.837 " "
Glucose	. . .	6.6	"	= 178.2 " "

Acetone and diacetic acid reactions faintly positive. Urobilin and indican absent. Leucin, tyrosin, and melanin not found.

Urine of May 30: Colour, bright orange-red. The orange-coloured pigment appeared to be a derivative of urobilin. Reaction faintly acid. Sp. gr. 1,032. Albumin present, 0.025 per cent. Sugar, 6.36 per cent. Blood present. Diacetic acid absent.

Microscopically: Pus cells present, no casts, red-blood cells present. Gram-negative, motile bacilli were seen, and in cultures there was an abundant growth of a coliform bacillus, and a few streptococcal colonies.

Urine of May 31: Sp. gr. 1,024. Acid. Albumin present, 0.8 per cent. Sugar, 4.4 per cent. Blood present. Diacetic acid absent. Bile-pigment and indican.

Urobilin gave a well-marked reaction.

Total nitrogen	. . . . .	0.57 per cent.
Ammonia nitrogen	. . . . .	0.065 "
Urea	. . . . .	0.97 "
Chlorides	. . . . .	0.65 "
Phosphates	. . . . .	0.17 "

Microscopically: Some epithelial cells, many leucocytes, some red-blood corpuscles. Mucus present.

#### *Examinations of the blood. April 23.*

Red-blood cells	. . . . .	4,500,000 per c.mm.
Leucocytes	. . . . .	7,300 "
Polymorphs	. . . . .	3,650 " 50 per cent.
Lymphocytes	. . . . .	3,524 " 48 "
Eosinophils	. . . . .	32 " 0.5 "
Large mononuclears	. . . . .	94 " 1.5 "
Basophils	. . . . .	0 " 0 "
Haemoglobin (Autenrieth and Königsberger)		95 "
Colour index	. . . . .	1.05

#### *April 26.*

Haemoglobin	. . . . .	83 per cent.
Iron in blood	. . . . .	0.048 per cent. (normal = 0.042 per cent.).

May 21. (After paracentesis abdominis.)

Haemoglobin . . .	94 per cent.
Iron . . . . .	0.056 per cent.

(The two last examinations were made by Dr. P. C. H. Fowell.)

On May 2 Wassermann's reaction gave a negative result.

*Examination of the ascitic fluid.* Total quantity 11.016 litres. Sp. gr. 1.005.

A pale citron-coloured, opalescent fluid, of alkaline reaction. Total solids, 1.658 per cent. Inorganic ash, 0.602 per cent.

Total nitrogen . . .	0.168 per cent.	
Albumin (Aufrecht) . .	0.47	"
Glucose . . . . .	0.186	" = 20.5 grammes, total.
Mucin present.		
Urea present.		
Cholesterol absent.		

*Examinations of the faeces.* April 22.

A firm, brown, constipated motion. Reaction alkaline. Urobilin reaction faintly positive. Blood absent. Mucin absent.

Microscopical: A few muscle fibres seen. Very few fat globules. No elastic fibres seen.

Fatty substances (Soxhlet)—

Total fat . . . . .	32.2 per cent. of dry faeces, by weight.
Neutral fat and fatty acids (free)	11.7 " " " "
Soaps . . . . .	20.5 " " " "

May 31. (Examination by Dr. Cammidge.)

A dark yellow, soft, solid motion. Strongly alkaline. Fairly well-marked urobilin reaction. Blood absent. Tests for ferments: Casein digestion normal; starch digestion normal.

Organic matter . . . . .	73.9 per cent. of dried faeces.
Total fat . . . . .	27.8 " " "
Neutral fat with free fatty acids .	5.8 " " "
Soaps . . . . .	22.0 " " "
Organic matter, not fat . . .	46.1 " " "
Inorganic ash . . . . .	26.1 " " "

*Iron in faeces, skin, and organs.* In 5 gm. of dried faeces, no iron was found.

In the blood the percentage of iron amounted to 0.048 (normal = 0.042 per cent.). Later, after paracentesis abdominis, the iron reached 0.056 per cent.

A portion of skin yielded a well-marked Prussian blue reaction, indicating free iron.

At the post-mortem examination:

The heart muscle showed a pronounced Prussian blue reaction. The marrow of the ribs and the muscles of the chest-wall showed no iron reaction. In the intestinal wall the reaction was feeble, but the reaction was conspicuous in the wall of the stomach.

The liver and pancreas showed a well-marked blue reaction. A quantitative estimation of the iron in the liver gave a total content of 32.8 gm.

*Tests of pancreatic efficiency.* As a test of lipolytic activity in the duodenum a stearin capsule, containing 5 gm. of potassium iodide, was administered by the mouth, and the saliva and urine were subsequently tested for the presence

of iodide. The absence of iodide indicated insufficient digestion of fat, and failure of the pancreatic juice to dissolve the stearin.

Schmidt's test of protein digestion : At 3 p.m. and at 8 p.m. on April 30, three small cubes of beef, enclosed in fine silk bags, were given by the mouth. In the faeces of the following day, many swollen silk fibres were seen, and a few muscle fibres exhibiting distinct striation, and well-defined nuclei. This indicated insufficient tryptic activity.

Cambridge's test was negative on three occasions (*vide supra*).

Löwi's adrenalin mydriasis test was positive. Pronounced dilatation of the pupil resulted when a few drops of 1 in 1,000 solution of adrenalin were introduced into the conjunctival sac.

Fat content of faeces, and amount of lipolysis : As will be seen on reference to the analyses quoted on p. 135, no evidence was forthcoming of failure of fat splitting, nor of any considerable failure of absorption of fat.

Tests for ferments in the faeces : Casein digestion by extracts of the faeces, estimated by Gross's method, indicated normal digestive power, but the value of this test is impaired by the fact that erepsin is also capable of digesting casein.

Estimation of diastase in the faeces (Wohlgemuth's method) : A normal diastatic index was obtained.

Glycosuria : The excretion of sugar in this case may be regarded as an indication of disease of the pancreas. There was no obvious response to limitation of the carbohydrate intake, and the percentage and total output of glucose in the urine remained practically unchanged, until the appearance of pus in the urine on May 29.

Thus it will be seen that of the eight tests of pancreatic efficiency which were carried out, four, namely the stearin capsule and Schmidt's tests, the adrenalin ocular test of Löwi, and the presence of glycosuria, pointed to a deficient activity of the pancreas. The remaining four, namely, Cambridge's test, the fat analyses of the stools, and the tests of the tryptic and diastatic activities of the faeces, gave results indicative of normal performance of the pancreatic functions.

This would suggest that the amount of pancreatic glandular tissue which remained functionally active sufficed for the production of adequate quantities of lipase and diastase, and probably of trypsin also, unless the tryptic powers of the faeces can be ascribed to erepsin alone.

But the functions of the pancreas as a gland of internal secretion appear to have been more severely impaired, as witness the presence of glycosuria and the dilatation of the pupil by adrenalin. Or, regarding the facts from another standpoint, these two tests proved more delicate than the others for the indication of pancreatic insufficiency.

It is not easy to explain the negative indication of Cambridge's test in a case in which the pancreas was the seat of so gross disease, save on the assumption that the value of a negative indication is little or nil.

*Post-mortem examination* (by Dr. H. Thursfield). June 18, 1912, twenty-eight hours after death. Body of a thin man, skin a peculiar tint of a dingy grey.

Examination of head and neck not allowed.

*Chest.* Very little fluid in pleural cavities. Oesophagus natural, no discoloration. Larynx, trachea, and bronchial glands natural.

*Lungs.* Right, 29½ oz. Left, 24 oz. Both oedematous. A few pleural adhesions on both sides. No consolidation, no tubercles.

*Heart.* 13½ oz. Chambers all much dilated. Valves normal. Heart muscle gave a very good Prussian blue reaction. Aorta and vessels—intima good, no marked atheroma. Marrow of ribs and muscle of chest-wall showed no Prussian blue reaction.

*Abdomen.* On opening the abdomen, after removal of a large quantity of slightly turbid fluid, the peritoneum was seen to be throughout of a dusky grey

colour, both visceral and parietal portions showing this tint. There were many adhesions, the omentum was shrivelled, and some of its adhesions had caught up the lower part of the gall-bladder, causing it to lie anterior to the liver and almost transversely across the right hypochondrium. There was, however, no obstruction. The intestines were all of a slate-grey colour, both on their external surface and within; the Peyer's patches and solitary follicles stood out deeply pigmented. The Prussian blue reaction was feeble.

The stomach mucous membrane was deeply pigmented, and showed a good iron reaction.

Liver, 57 oz. Tint of surface of section a deep-brown colour; substance firm but not markedly fibrotic. Surface showed some perihepatitis, and gave a good Prussian blue reaction.

Spleen, 4 oz. Deeply marked by perisplenitis. Adhesions had fastened it high up under the diaphragm.

Pancreas. Much adhesion of the surrounding tissues; a few small patches of fat necrosis. The pancreas itself was soft, misshapen a little by the firm adhesions, and on section of a deep-brown colour. It gave a good iron reaction (Prussian blue).

Suprarenals: natural; iron reaction not tested.

Kidneys, 22 oz. Large, soft, infiltrated in every direction with purulent streaks and small abscesses both in pyramids and cortex; pelves injected and thick.

The kidney tissue did not show a good iron reaction.

Ureters: natural, not dilated.

Bladder, large. The mucous membrane showed marked capillary injection and some swelling.

Organs of generation: natural.

Joints: natural.

*The metabolism of iron* (R. L. M. W.). A general review of the iron metabolism in bronzed diabetes, as far as is known, has already been given, and it only remains to discuss briefly the results obtained in the light of these different views. It is quite clear from previous observations, and our own, that the iron deposited in the tissues does not originate from excessive destruction of blood; and so we have to look for some other source of this element. Attention has been particularly directed to the cell proteins as a possible explanation, and more especially the nucleo-protein moiety. Iron occurs in nucleo-proteins apparently in organic combination, since these substances do not give the Prussian blue reaction, ammonium sulphide test, or haematoxylin staining. The iron can, however, be demonstrated by the use of appropriate reagents, and it is then present in an ionized state. A further proof has been given by Botazzi, who demonstrated that extracts of the hepatic nucleo-proteins yield ionized iron as the result of autolysis. The exact nature of the combination of iron in nucleo-proteins is not understood, but it is significant to note that plasminic acid, and the complex phosphoric acid derivative of nucleo-proteins, are capable of 'masking' iron. More recently Sprunt, Colwell, and Hagen have demonstrated experimentally the liberation of iron and pigment formation in the liver during autolysis. These pigments, both iron-containing as well as other kinds, they assume are formed by self-digestion of the parenchymatous cells of the organ.

The pigments present in the organs of cases of haemochromatosis have been



divided into two classes, viz. haemosiderin, the iron-reacting pigment; and haemofuscin, the non-iron-reacting pigment. The recognition of the first type depends entirely on the reactions for iron which it readily gives. Haemofuscin, on the other hand, is identified mainly by its morphological characters, and the absence of the reactions for iron.

In view of the divergence of opinion with regard to haemofuscin, and the lack of evidence as regards its physical and chemical properties, it does not seem justifiable to retain this name. Abbott found that on using heated hydrochloric acid the so-called haemofuscin pigments also gave the reactions for iron, the only exception being the pigment granules in the muscle cells. It would seem highly probable, therefore, that a large number of pigments have been included under this designation on purely arbitrary grounds. The proteins and certain fractions of their break-down products are capable of producing very definite pigments, as instance the darkening of globulin precipitates when separated from blood serum by fractional precipitation with ammonium sulphate. We would suggest such a possibility in the case of haemochromatosis, since we do not find any marked evidence of extensive protein destruction in this disease. The metabolism of iron has apparently undergone some error whereby it is retained in the cell and not excreted. That iron is retained in the organs is strikingly demonstrated by reference to the analytical figures given below:

	Liver. %	Pancreas. %	Glands. %	Spleen. %	Bile. %	Heart. %
<i>Normal</i>						
(Hopkins)	0.08 to 0.18	—	—	0.09	—	—
<i>Haemochromatosis</i>						
Anschutz	7.62 (55.7 total)	5.0 (44 % Ash)	14.6 (Ash 58.36)	—	—	—
Hess and Zerkelle	7.1 (38.7 total)	—	—	—	—	—
Jeanselime	1.040	—	0.317 (thyroid)	0.169	0.012	0.181
Auscher and Lapique	1.13 (fresh tissue)	—	1.85 (fresh)	0.42 (fresh)	—	—
Garrod	2.05 (32.8 grm. total)	—	—	—	0.00	—
<i>Pernicious Anaemia</i>						
Quinke	2.1	—	—	—	—	—
Ryffel	0.18 (1.01)	—	—	0.18 (0.44)	—	0.088 (0.051)

These findings receive corroboration from the examination of the histological preparations, and the distribution of the pigment within the tissues. Not only do we find this increased iron content in this disease, and also in allied conditions, but another feature which would appear as characteristic of haemochromatosis alone presents itself. The case we have described showed a complete absence of iron in the urine, bile, and faeces, and, on the other hand, a slight excess of iron in the blood. This extraordinary avidity of the tissues for iron is also clearly



demonstrated by the occurrence of the iron-containing pigment in the secretory cells, and not in the excretory cells, and this more especially in the kidneys. The view of Parker, enunciated in 1903, thus receives support, although a defective iron secretion does not explain all the facts. As a result of our work, three main features appear to be characteristic of this disease, viz. (1) the enormous quantities of iron deposited in the tissues; (2) the great avidity of the tissues for iron; (3) the marked retention of iron in the cells even when in an ionized condition, and its absence from the excreta.

Although we recognize that there are still many gaps in our knowledge of the metabolism of iron, it may be justifiable to suggest a working hypothesis.

The changes in the liver are regarded as the primary event, resulting in an abnormal transport of iron, either in a non-metabolized form, or in a form with which the cells are incapable of dealing. The iron is thus deposited in the various organs, the avidity of which for this element is fundamental, though obscure. The blood evidently does not require the iron, and the cells seem incapable of excreting it, and consequently it accumulates in the body. Unfortunately we have no experimental proof at present that the intestinal mucous membrane would absorb large quantities of iron when administered by the mouth in cases of haemochromatosis. The origin of the deposited iron we would assume to be entirely from some protein complex, possibly of the nature of a nucleoprotein, and not from haemoglobin or its derivatives. Further, the iron-containing pigment, haemosiderin, in my opinion, represents only one stage in the metabolism of this protein complex, the so-called haemofuscin and allied pigments being closely related types. A study of pigmentation along these lines, together with an extended knowledge of the transport and metabolism of iron-containing proteins, is urgently called for before we can lay down any definite hypothesis to correlate the clinical syndrome met with in this disease.

*Histological examination of the skin* (by Dr. H. Adamson). Pieces of skin were fixed and hardened in alcohol, and cut in paraffin, and the sections were mounted (1) unstained, (2) stained with alum-carmin, (3) treated with ferrocyanide of potassium (2 per cent.) for one hour, with hydrochloric acid (1 per cent.) for one hour, and stained with alum-carmin, (4) stained with polychrome methylene blue.

Sections 1 and 2 showed the epidermis much thinned. It was reduced to from three to five layers of cells, and the prickles were shrunken. There was complete absence of fat from the subcutaneous tissue, and no sebaceous glands were seen, although hair follicles were present. There was a marked deposit of pigment in the epidermis, in the form of brown granules, which filled the two lowest layers of epidermal cells. In the upper part of the corium, a little below the epidermis, there were, here and there, connective-tissue cells filled with brown pigment granules, and some of the endothelial cells of the capillary blood-vessels also contained similar granules. The most abundant deposit of pigment was, however, in the deeper part of the skin in the neighbourhood of the sweat glands. Here there were wide transverse bands of pigment between the deeper

layers of the corium and the subcutaneous tissue, i. e. in the position which would have been occupied by the fat cells had they been present. The pigment in these bands was collected in large round or oval masses, between which were cells of the connective-tissue type, many of them filled with pigment granules. The larger masses were apparently also cells stuffed with pigment granules, the cell-nucleus being hidden by the pigment, which was in many masses so dense as to appear almost black. The cells of the sweat glands and the connective-tissue cells around them were also filled with pigment granules.

In (3)—sections treated with ferrocyanide of potassium—the pigment in the two layers of cells of the epidermis remained unaltered in colour, while the pigment in the corium, i. e. in the connective-tissue cells and endothelium of capillaries, in the sweat glands, and in the transverse bands at the deeper part of the section, stained of a deep blue colour, indicating that the pigment in the epidermis was iron-free (melanin), while that in the corium was iron-containing (haemosiderin).

In (4)—polychrome methylene blue—all the pigment granules were stained a greenish tinge. This distinguished the pigment cells of the upper part of the corium from 'mast-cells', to which they bore a morphological resemblance, mast-cell granules staining red with polychrome blue. Although there was perhaps a slight increase of connective-tissue cells in the upper part of the corium, there was nothing to indicate that inflammatory reaction had preceded or followed the deposit of pigment.

#### *Histological Examination.*

By J. F. Gaskell<sup>1</sup> and P. T. Vaile.

*Method.* All tissues were hardened in formol Müller (10 per cent. formalin added to Müller's solution) for forty-eight hours, and then transferred to Müller's solution and kept in this for at least a week, or until required. The tissues were then treated in two ways:

- A. Dehydrated with alcohol, cleared in cedar-wood oil, and embedded in paraffin in the ordinary way.
- B. Embedded in gelatin according to the method already described by one of us<sup>2</sup> and cut whilst frozen.

The following stains were employed for each tissue:

*For gelatin sections*—Mayer's haemalum and watery eosin, haemalum and Sudan III. *For paraffin sections*—haemalum and alcoholic eosin, haemalum and van Gieson, Weigert's elastic stain, and Nishimura's (9) method for iron counterstained, if desired, by alum-carmin.

Nishimura's method is the following: Paraffin sections are brought down to

<sup>1</sup> Working under the tenure of a Beit Memorial Fellowship.

<sup>2</sup> 'A Method of Cutting Frozen Sections by Embedding in Gelatine', by J. F. Gaskell, *Journal of Pathology and Bacteriology*, 1912, xvii, 58.

water in the usual way, and are then placed for one hour in a solution of strong ammonium sulphide. They are then thoroughly washed in distilled water, and placed in a mixture of equal parts of freshly-made 2 per cent. potassium ferrocyanide and 1 per cent. hydrochloric acid for twenty minutes. They are then washed in 0.5 per cent. hydrochloric acid and again thoroughly washed in distilled water and placed, if desired, in the counterstain. They are finally dehydrated and mounted in Canada balsam in the ordinary way.

The most striking appearances found *post mortem* were—The fibrosis and deep-brown pigmentation of the liver and pancreas; the intense pigmentation of the thyroid gland, suprarenal glands, and heart muscle; and pigmentation of the skin.

The following is the detailed description of the macroscopical and microscopical appearances found in the various organs:

*Liver. Macroscopical appearances.* The gall-bladder was found to be caught up by adhesions of omentum so as to lie anteriorly to the liver, and almost transversely across the right hypochondrium. There was, however, no obstruction of the duct. The liver weighed 57 oz. Some perihepatitis was present. The surface was irregularly nodular, and the whole organ was of a remarkable brown colour. The substance was firm, but did not seem markedly fibrotic on section. The cut surface was of a deep-brown colour and gave a good Prussian blue reaction.

*Microscopical appearances.* Throughout the organ, scattered amongst the lobules and interlobular tissues, collections of organisms are seen. Those in the lobules are surrounded by extensive areas of necrotic liver tissue, containing a considerable amount of diffuse fat. Probably all areas of the degeneration observed are due to the terminal septicaemia. Haemorrhages are also seen with a similar distribution, and are presumably due to the same cause. These appearances can be set aside in considering the microscopical picture of haemochromatosis. The whole liver shows a very great increase of fibrous septa, in which the markedly dilated veins (Pl. 13, Fig. 1, *p.v.*) are very conspicuous; the lobules are very irregular in size and shape, owing to their greater or less destruction by the new fibrous tissue.

The hepatic veins are difficult to observe, but those identified were found lying in the centre of the surviving liver tissue. The hepatic artery shows some thickening of its intimal layers, which is fibrous in nature; the muscle of the artery walls contains a brown pigment in its fibres which does not give the Prussian blue reaction for iron. This pigment is probably identical with the haemofuscin of Sprunt and other authors. It is found in the arteries of all organs examined.

The fibrous tissue is invading and replacing the outer region of the lobules, cutting off cells in small groups or singly, the groups being frequently formed of a double row of small flattened cells having somewhat the appearance of bile-ducts. These have been called, in previous descriptions of this condition, pseudo bile-ducts (Pl. 13, Fig. 1).

Bile-ducts proper (Pl. 13, Fig. 1, *b.d.*) also are numerous in the thick strands of fibrous tissue.

This new fibrous tissue contains a moderate number of nuclei and a con-

siderable amount of elastic tissue. It is therefore probably of fairly slow growth. It contains here and there considerable collections of round cells; also a large amount of coarse pigment scattered diffusely through it. This pigment will be described in detail shortly.

The intercellular capillary spaces are very conspicuous. This is partly due to the congestion of the terminal septicaemia, but is also due to increase of fibrous tissue, and to the great prominence of Kupffer's cells (Pl. 13, Fig. 1, *k.*), owing to the presence of a coarse pigment in their protoplasm similar to that in the connective-tissue septa. This pigment stains deeply with Nishimura's stain for iron.

The liver cells themselves are mostly smaller than normal, but vary greatly in size, as also do their nuclei. Cells with large nuclei are occasionally met with. No mitoses have been found.

The protoplasm of the cells is granular, and takes a diffuse fat stain, but is remarkable for the absence of fat globules.

Practically all the liver cells contain pigment, the amount of which increases according to the distance from the centre of the lobule; the cells right at the periphery, which are being cut off by the fibrous tissue, contain large amounts. The pigment tends to collect in that part of the cell which is most distant from the blood capillaries; that is to say, in the region of the bile capillaries. In some cells it is also specially aggregated round the nuclei. This pigment in the liver cells is very finely granular, and all stains deeply with the iron stain. The very highly pigmented peripheral cells have well-staining nuclei, although their protoplasm is small in amount. The cells forming the pseudo bile-ducts, and lying isolated in the fibrous tissue, are even more deeply pigmented, their protoplasm being still smaller in amount. This pigmentation and atrophy may be seen in all stages down to complete degeneration. In the latter case a collection of granular pigment is all that remains.

The smaller bile-ducts proper also contain pigment in their lining cells. This pigment is in somewhat coarser granules than that in the liver cells, though it is still fine. It all gives the iron reaction. The larger bile-ducts vary; some containing a considerable amount of pigment, others—and these on the whole the largest—being pigment-free. The pigment in the fibrous tissue (Pl. 13, Fig. 1, *p.*) is very coarsely granular, and takes the stain for iron very deeply. It appears frequently to be extra-cellular, lying in lymphatic spaces, but also frequently lies in connective-tissue cells. Iron-containing pigment is also found in the walls of the larger veins, being mostly in the fibrous wall; also occasionally in their endothelial cells. Cells are also seen lying free among red-blood cells in the lumen, which are highly pigmented, and are possibly desquamated endothelial cells. The smaller veins also occasionally show slight pigmentation in their walls.

In the liver, therefore, the iron pigment compound is accumulated in the liver cells around their bile capillaries. This leads to atrophy and destruction of the liver cell, and at the same time gives rise to a chronic inflammatory reaction of the perilobular fibrous tissue: the pigment being finally either stored in the fibrous tissue cells or carried off in lymphatics. The pigmentation also extends down the bile-ducts, but the chemical evidence given elsewhere that no iron is contained in the bile shows that there is almost complete retention of the substance in the liver cells themselves. The presence of iron in the Kupffer cells shows that iron pigment is circulating as such in the capillary blood-vessels.

Areas of regeneration, as described by Sprunt, have not been observed.

*Kidneys. Macroscopical appearances.* Weight of the two kidneys together, 22 oz. They were large and soft and infiltrated with purulent streaks and small abscesses in all directions, both in the medulla and cortex;

the pelves were injected and thickened; the ureters were natural, showing no dilation. The cut surface did not show a marked Prussian blue reaction.

*Microscopical appearances.* The kidney is partially destroyed by pyelonephritis. Abscess cavities are seen surrounded by an intense infiltration with polymorphonuclear leucocytes, which extends widely through the kidney substance. The rest of the kidney shows a most intense congestion of capillary vessels.

The main vessels and their branches are normal. The glomeruli (Pl. 13, Fig. 2, *g.*) are all congested; the nuclei of the glomerular epithelium are normal, the cell protoplasm contains scattered, small granules of fat, and also a finely granular pigment (Pl. 13, Fig. 2, *p.*) which is widely diffused throughout the glomerulus, and gives an iron reaction strongly. The Bowman's capsules appear to be unaltered, and do not contain pigment; but occasionally their cells contain fat. The convoluted tubules of the first order (Pl. 13, Fig. 2, *t. 1*) are somewhat widely dilated, the lumen being filled with granular debris. The cells themselves appear flattened and irregular, and occasionally their nuclei do not stain well. They take a faint pink stain with Sudan III. The protoplasm is very granular in appearance, but no trace of iron-containing pigment has been observed in these cells. Here and there tubules are seen filled with blood. The convoluted tubules of the second order (Pl. 13, Fig. 2, *t. 2*) stand out very conspicuously in a section stained for iron, as the protoplasm of their lining cells is loaded with a pigment staining deep blue by this method. Their nuclei appear normal. The cells themselves are occasionally somewhat increased in size owing to the pigment present in them. They often also contain a considerable amount of fat. The interstitial tissue is not generally increased, but iron-containing pigment is occasionally seen in it. The pigment occasionally extends for a short distance down the ascending loop of Henle; with this exception the medulla is completely pigment-free.

This distribution of the pigment in the convoluted tubules of the second order only, and the complete freedom of those of the first order from it, has been confirmed by serial sections. The histological picture of the kidney in haemochromatosis is greatly obscured by pyelonephritis. The swelling and congestion of the organ are undoubtedly due to the latter cause, as also the condition of the convoluted tubules of the first order.

The probable explanation of the distribution of the iron-containing pigment in the glomerular epithelium and in the convoluted tubules of the second order is, that this substance is excreted through the glomeruli, and reabsorbed in the convoluted tubules of the second order; the presence of the fat in the latter is physiological.

That the function of the secondary tubules is to reabsorb is becoming more and more probable on pathological evidence. The presence of large quantities of pigment here, therefore, is, on these lines, reconcilable with the chemical evidence in this case that even the normal amount of iron was absent from the urine.

The path of excretion through the glomeruli, and the entire absence of any excretion through the convoluted tubules of the first order, is in marked contrast with the condition found in pernicious anaemia, in which iron is found abundantly in the convoluted tubules of the first order, and is practically confined to these.

There is, therefore, as regards the path of excretion, an essential difference between haemochromatosis and a true disease of the blood and blood-forming organs. The blood in this case, as in most other recorded instances of the disease, was practically normal.

*Pancreas. Macroscopical appearances.* The organ was very adherent to surrounding structures. It was soft, and somewhat misshapen, owing to firm



adhesions. A few patches of fat necrosis were present. On section the organ was of a deep-brown colour; a good Prussian blue reaction was obtained.

*Microscopical appearances.* The whole pancreas shows a very large increase in fibrous tissue (Pl. 13, Fig. 3, *f.t.*), dividing up the parenchyma into small irregular lobules, which are in various stages of degeneration. This fibrous tissue contains an enormous quantity of brown pigment, both contained in fibrous-tissue cells and lying extra-cellularly in masses. This pigment all shows an intense iron reaction.

The blood-vessels are normal, except for the presence in their walls of a considerable amount of yellow pigment lying in the muscle cells. The condition is similar to that already described in the arteries of the liver; the pigment does not stain for iron.

Elastic tissue is not conspicuous in the new fibrous tissue. The ducts (Pl. 13, Fig. 3, *d.*) lying in fibrous tissue appear normal and usually contain no pigment; occasionally, however, one is found containing a certain amount of it.

The pancreatic tissue itself is irregularly degenerate (Pl. 13, Fig. 3, *p.*). The better parts show fairly normal cells containing a large amount of iron-containing pigment; the granules of this pigment vary greatly in size.

Other portions of the pancreatic tissue are completely degenerate. Cells can no longer be made out, and the whole tissue is represented by a granular mass, containing large quantities of iron-staining pigment in granules of various sizes. These degenerate areas take a diffuse fat stain; other portions of the organs show grades between these two extremes.

Certain areas of tissue, which are in all probability islets of Langerhans (Pl. 13, Fig. 3, *l.*), often appear to be better preserved than the surrounding tissue. They are conspicuous owing to the presence of considerable quantities of fat in them, and are also all more or less pigmented, the pigment lying most abundantly in the walls of the capillary vessels of the islet. Some of these areas are very highly pigmented and markedly degenerate. The section described was taken from about the middle of the organ. No sign of acute inflammation, such as acute congestion or haemorrhage, was found in the organ.

The question whether the degenerate areas in the pancreas are to be attributed to the terminal septicaemia or not is difficult to decide. The absence of any acute inflammatory reaction in the sections, however, makes it probable that all the lesions found are due to the chronic condition of haemochromatosis. The pigmentation is the more marked the more degenerate the cells appear. The great fibrosis is, as in the liver, probably secondary to the pigmentation and destruction of the parenchyma of the organ. The islets of Langerhans are undoubtedly involved in the general degeneration, the islet shown in Pl. 13, Fig. 3 being the best preserved one found in all the sections examined. It may also be noted that paraffin sections of the tail of the organ showed an even more intense pigmentation than those of the head end; but the preservation of this tissue was not sufficiently good to speak with certainty about the condition of the islets here.

The evidence therefore tends to show that the diabetes present was due to disease of the pancreas. The fact that cases of haemochromatosis occur in which diabetes is not present shows that diabetes is rather to be looked upon as an incident in the condition, depending upon the severity of the disease of the pancreas.

*Heart. Macroscopical appearances.* The heart weighed 13½ oz. All the chambers were much dilated, and the valves were normal; the heart muscle was dark in colour, and gave a very marked Prussian blue reaction. The aorta and vessels showed no marked atheroma, and their intima was good.

*Microscopical appearances.* There is marked congestion of the veins and capillary vessels (Pl. 14, Fig. 4, *c.*), and here and there haemorrhages of small dimensions.



The interstitial tissue is not generally greatly increased, but occasional areas are met with showing increased fibrous tissue dividing up the muscle fibres. This new fibrous tissue contains a certain amount of fine elastic fibres. The muscle fibres (Pl. 14, Fig. 4, *m.f.*) in both paraffin and gelatin sections show pigmentation, the fibres being broken across especially frequently where the deposit is thickest.

Striation is clearly seen, especially in the gelatin preparations. A finely granular pigment is present, to a greater or less extent, in all the muscle fibres. It gives the iron reaction very strongly. It is especially aggregated round the nuclei, in a spindle-shaped manner, but also lies throughout the muscle fibre, arranged in longitudinal rows. The amount present is so great that the section stained by Nishimura's method appears bright blue to the naked eye.

A similar, but coarser, pigment is also found lying between the muscle fibres, either in connective-tissue cells or free in lymph spaces (Pl. 14, Fig. 4, *p.*).

The arteries show a brown pigment in their muscle entirely unaffected by the iron stain, similar to that in other organs.

The heart muscle also shows fat in a considerable number of its fibres, distributed diffusely in company with the pigment. The fat globules are extremely fine, and only present in small quantity. The pigment, therefore, seems to be stored especially in the heart muscle. The fragmentation of the muscle fibres may be artefact, but it is suggestive that it occurs where the muscle fibre is most heavily loaded with pigment.

The interstitial coarse pigment probably lies mostly in the lymphatics draining the heart muscle.

*Lung. Macroscopical appearances.* Right lung weighed 29½ oz. Left lung weighed 24 oz. Both were oedematous, and there were a few pleural adhesions on both sides. There was no consolidation, and no sign of tuberculosis.

*Microscopical appearances.* The veins and capillaries are congested, and considerable oedema is present. In the oedematous fluid in the alveoli there are frequently present a number of cells with a round nucleus and considerable protoplasm. This protoplasm frequently contains granules of pigment of varying sizes; other cells show no pigment, but contain a considerable amount of fat; others, again, contain both pigment and fat. These cells are probably cast-off alveolar epithelium; other similar cells still *in situ* also contain pigment and fat. This pigment stains by the stain for iron.

Coal pigment is present in the connective tissues round the bronchi, but there is no sign of iron-containing pigment here. The pleura also contains coal pigment, but is otherwise normal. The elastic tissue in the lung is normal. The muscle of the walls of the arteries contains the iron-free yellow pigment seen in other organs.

This condition of the lung has in all probability no connexion with haemochromatosis, but is merely due to back-pressure from cardiac insufficiency. In favour of this is the absence of any increased fibrosis or interstitial pigmentation.

*Spleen. Macroscopical appearances.* The organ weighed 4 oz.

Adhesions had fastened it high up under the diaphragm. It was deeply marked by perisplenitis.

*Microscopical appearances.* The arteries show slight arterial sclerotic thickening of the intima, with an irregular increase of elastic tissue. The muscle of their walls shows the yellow-brown pigment which does not contain iron, which has been observed in the other organs.

The larger veins in the trabeculae appear somewhat widely distended.

The Malpighian bodies appear to be about normal in size and distribution, but contain a considerable quantity of brown pigment in coarse granules; this pigment shows the iron reaction strongly; it lies in the supporting cells, and possibly also free between them.

The splenic pulp shows areas with broad sinuses filled with blood, which are about normal in amount. Throughout the pulp there is a diminution in round cells, with a considerable increase in reticular cells with large oval nuclei.

Iron-containing pigment is diffusely scattered throughout this tissue. It lies either in the reticular cells, or occasionally free in the sinuses. There is a diffuse connective-tissue increase throughout, and nodules of pigment also lie occasionally in this tissue.

The trabeculae also contain scattered pigment of a similar nature, but in rather coarser granules.

The spleen, therefore, shows a diffuse pigmentation, with an accompanying diffuse fibrosis and increase of reticular tissue. The proportion of the various tissues is not otherwise much altered.

*Suprarenal. Macroscopical appearances.* Natural. The Prussian blue reaction was not tried.

*Microscopical appearances.* The cortex and medulla have their normal relative proportions. There is considerable congestion of the organ, and certain areas show degenerative changes often associated with groups of organisms lying at their centre. These changes may be put down to the terminal septicaemia. These areas occur both in cortex and medulla.

*Cortex.* The cells are small, possibly owing to the congestion of the inter-cellular capillaries. Fat is distributed irregularly, the outer zona glomerulosa containing but little, the middle zona fasciculata a moderate amount, and the inner zona reticulata containing a large quantity. The scattered islets of cortical cells in the medulla also contain a large amount of fat. The doubly refractile substance has a similar distribution, being practically absent in the glomerulosa, present to some extent in the fasciculata, and present in quantity in the reticulata.

Pigment is mainly confined to the zona glomerulosa, though occasionally a group of cells extending into the fasciculata contain it. It is present in great quantity in the outermost zone, and tends to aggregate round the nuclei of the cells in this region. Thus there seems to be an antagonism between the pigment and the fat and doubly refractile substance of the cortex; occasionally, however, fat and pigment are present in the same cell.

*Medulla.* The medullary cells show the chrome reaction fairly well; in addition to this, another yellow-brown pigment is seen which has not been observed for certain in the medullary cells, but lies rather in the connective tissue between these, which is diffusely increased. This increased connective tissue shows also fine elastic fibres running through it. The pigment in the connective tissue, which is mainly in the cells themselves, all stains deeply with the iron stain.

The capsule of the gland also contains pigment of a similar kind, both in cells and also in what appear to be lymph spaces.

The distribution of the pigment in the suprarenal gland is almost exactly that of the intravital staining obtained by Goldmann (5) in this organ.

The amount of the normal constituents of the cortex, fat and doubly refractile substance, is moderate; there seems to be some displacement of these substances towards the inner zones by the accumulation of pigment in the outermost zona glomerulosa. The normal brown pigment found in the zona reticulata is, if present at all, very scanty.

The increase of fibrous tissue in the medulla is probably due to the pigment accumulating there.

The areas of degeneration, and the great congestion of the organ, are to be referred to the terminal septicaemia.

The pigment in the capsule is probably along the course of the lymphatics draining the organ.

*Thyroid and parathyroid glands. Macroscopical appearances.* The gland is normal in size and shape, but is of a deep brown colour.

*Microscopical appearances.* The amount of fibrous-tissue stroma is about normal; no pigment is found in this.

The glandular structure consists of alveoli of very varying sizes, lined by a single layer of epithelium, which is much more flattened in the larger alveoli than in the smaller ones.

The epithelial cells (Pl. 14, Fig. 5, *e*.) appear normal, except for the presence of a large amount of iron-containing pigment in all of them, which is present in greatest amount in the large cells lining the small alveoli. It is all in a finely granular state. The alveoli contain colloid secretion (Pl. 14, Fig. 5, *c*.) in various states; in some of the smaller it is in small globules roughly of the size of red blood corpuscles; in the larger it is in the form either of globules of very irregular size or in one uniform mass. This colloid material in the alveoli contains the remains of cells, probably cast-off epithelial cells, which are heavily pigmented, and also pigment (Pl. 14, Fig. 5, *p*.), which has become free by disintegration of cast-off cells.

Here and there the alveolus is seen with groups of minute fat globules in it, possibly remains of cells which have undergone fatty degeneration.

As in other organs, the large arteries show the iron-free yellow-brown pigment.

The parathyroid shows a patchy distribution of pigment in its cells. It is otherwise normal.

*Thymus gland. Macroscopical appearances.* Small and atrophied.

*Microscopical appearances.* There are here and there remains of glandular tissue lying in a loose fibrous tissue. An occasional Hassall's corpuscle is seen embedded in rounded cells of the normal type met with in this gland. Certain groups of these cells contain a considerable amount of finely-divided iron-containing pigment.

Some of the branched connective-tissue cells also contain this pigment. As well as this they contain fat, some being considerably swollen up by it. They are apparently on the way to form the fat cells found in the completely atrophied part of the gland.

*Testis. Macroscopical appearances.* Normal.

*Microscopical appearances.* The secreting tubules (Pl. 14, Fig. 5, *t*.) are arranged in a normal manner; spermatozoa are not to be found in the lumen, the whole of which is filled with fat, which has the characters of ordinary neutral fat, showing no double refraction.

The lining epithelium is also normal, and contains no pigment.

The interstitial tissue is also normal in amount, the interstitial cells (Pl. 14, Fig. 6, *i*.) are conspicuous in containing doubly refractile fat; this property is not lost even in Sudan-stained specimens. These cells also contain pigment which gives the iron reaction.

The vessels (Pl. 14, Fig. 6, *v*.) are conspicuous, as they contain much iron pigment in their walls. This pigment lies both in their endothelial cells, and also in their walls. The larger arteries, however, only show the iron-free pigment present in this situation in all organs.

The presence of iron-staining pigment in the interstitial cells does not agree with the description given by Sprunt, who states that the pigment present in this situation does not stain for iron.

A comparison may again be made with the results of intravital staining by Goldmann's methods, in which the interstitial cells are also picked out by the stain.

The intestines were so far advanced in decomposition as to be useless for histological methods, so the presence of iron-containing pigment described by Sprunt in the glands of the mucosa of the stomach and duodenum could not be confirmed, nor the presence of iron-free pigment in the unstriated muscle coats.

Various groups of lymphatic glands were seen to be pigmented, but these were not obtained for histological examination.

To sum up : The condition appears to be one in which iron pigment is stored up in enormous quantities in the various glands of the body. In the case of the liver and pancreas this is associated with a secondary fibrosis of these organs, which, in the case of the latter organ, frequently gives rise to a secondary diabetes.

The thyroid, parathyroid, and suprarenal cortex also store the iron pigment in their secretory cells, but apparently without giving rise to any further change in these organs. The presence of the pigment in the suprarenal medullary cells is extremely doubtful, though Sprunt asserts that this occurs. There is, however, an interstitial pigmentation and fibrosis here which lends support to Sprunt's views.

The sub-maxillary glands, and mucous glands of the trachea also, are, according to Sprunt, pigmented. The presence of pigment in certain situations may be explained by its carriage in the blood to these situations, on the analogy of intravital staining and many pathological pigmentary conditions. Its presence in the Kupffer cells in the liver, in the cortical cells of the suprarenal medulla, and in the interstitial cells of the testis, and especially the pigmentation of the skin described elsewhere, all comes into this category. That the disease is not a blood disease is, however, shown by the normal condition of the blood found in this and many other cases, and also by the normal condition of the bone-marrow described by Sprunt and others. This is strikingly upheld by the distribution of the pigment in the kidney, the only explanation of which is the excretion of the pigment by the glomeruli and its reabsorption in the convoluted tubules of the second order; the condition in pernicious anaemia, essentially a blood disease, being, as already described, strikingly different.

The origin of the iron-free pigment in the walls of all the blood-vessels, the unstriped muscle of the intestine, and in the skin, is as obscure as its relation to the iron-containing pigment which is the preponderating cause of pigmentation.

In organs in which fibrosis is present attempts are being made to remove the pigment from them by lymphatic channels, and it is to this removal that the pigmentation of lymphatic glands is due.

The histological evidence of this disease, therefore, points to a metabolic derangement of, at any rate, iron-containing compounds, which leads to the accumulation of these in certain cells which are finally destroyed in the process.

#### *Concluding Notes.* (A. E. G.)

In many of the published accounts of cases of bronzed diabetes the clinical signs and symptoms, other than those which constitute the cardinal features of the syndrome, have received but scanty mention, but there were certain symptoms observed in our case which seem worthy of more than passing allusion, and are perhaps entitled to a not unimportant place in the clinical picture of the condition under discussion.

The quality of the pigmentation itself calls for further notice, for it differs from that of any other variety of discoloration of the skin with which I am familiar. Yet it is difficult to express in words wherein the peculiarity consists. The epithet 'bronzed', which has been applied, with less accuracy, to other varieties, such as arsenical pigmentation and that of Addison's disease, is specially applicable to the tint of bronzed diabetics, which has a quality which can only be compared to that of a metallic surface. Hanot and Chauffard speak of it as '*une teinte plombée uniforme, tout à fait terreuse, mais à reflets gris*

plus que bruns, quelque chose, en un mot, de tout à fait caractéristique'. And in another place they describe the skin as exhibiting 'quelques reflets plombés'. Barth's description is as follows: 'Ce n'était pas une coloration bronzée franche, mais plutôt une nuance d'un gris noirâtre, à reflets métalliques, rappelant celle de la fonte de fer, ou mieux encore de la plombagine qui sert à lui donner du luisant.' A tint which is so hard of description even in the French tongue offers even greater difficulties to one who writes in English, but the artist has succeeded in reproducing its peculiarities in his coloured drawing of our patient (Plate 12).

Again, the distribution of pigment is peculiar. In our case, as in most others, the pigmentation was more pronounced upon parts exposed to light and air—the face, the neck, the backs of the hands. The palms are usually much paler. The pigmentation was by no means evenly distributed, and ill-defined areas of darker tint were seen upon a paler ground. There was no pigmentation of the mucous membranes. This, too, is an almost unbroken rule in bronzed diabetes, although a grey tint of the gums has been observed as present in a few instances.

The somnolence and apathy, which were such pronounced features of our patient's malady, were present from the time of his admission to the hospital until his death. At first we were misled by them into supposing that the somnolence indicated the near approach of diabetic coma. Like symptoms have been noted in other cases. Troisier, who described an example of bronzed diabetes some ten years before it was recognized as a syndrome of morbid events, interdependent or dependent upon some common cause, wrote as follows of his patient: 'Il reste habituellement dans la somnolence et répond à peine aux questions qu'on lui adresse.' Fitcher also describes this phenomenon, which may be ascribed to the condition of extreme asthenia which is induced by the coexistence of two so grave morbid conditions as cirrhosis of the liver and diabetes. It pertains rather to the symptomatology of the former than of the latter.

Emaciation is another common feature of bronzed diabetes which was conspicuous in our case.

The special enlargement of the left lobe of the liver also, which formed a salient tumour, easily visible when the abdomen was uncovered, has been observed in other cases, and notably in those which Fitcher has described.

A good opportunity was afforded of estimating the value of the tests of pancreatic efficiency which have been devised of recent years, and some of these were accordingly tried. That the pancreas was the seat of grave disease we could have no doubt, in view of the findings in other cases of bronzed diabetes. Some of the tests in question indicate the activity or failure of the internal, and others of the external, secretions of the gland; and, seeing that the pancreas may be the seat of very diverse morbid processes, in various stages of their development, it is clear that we must not look to the tests for more than they can reasonably be expected to show, nor for an unequivocal answer to so crude



a question as whether the gland be sound or no. At any rate we must not expect an answer to this question from any single test. The frequent absence of glycosuria, even in cases of grave disease of the gland, warns us to be guarded in our inferences. As yet the tests, rather than the pancreas of our patients, are on their trial.

The positive outcome of Löwi's adrenalin mydriasis test in our case served to strengthen the favourable opinion of its value which other cases had led us to form, and which has since been still further reinforced: but undoubtedly there is still much to be learned as to its significance, and its indications are no more infallible than those of other tests. Our experience shows that the results of Löwi's test do not by any means run parallel with those of Cammidge's, which, in this case, afforded no indication of pancreatic disease. It is to be regretted that, when the case was under observation, we were not yet employing the urinary diastase test, which has since given very encouraging results in our hands in other cases in which pancreatic lesions were present.

It will be noted that, although the pancreas was so seriously damaged by disease, there was no evidence of greatly impaired activity of its digestive functions.

As regards the sequence of the morbid events which go to make up the picture of bronzed diabetes, it cannot be claimed that the work here recorded brings us very much nearer to the solution of the problem.

Of the three chief factors in the syndrome, cirrhosis of the liver, haemochromatosis, and glycosuria, it can hardly be doubted that the glycosuria, far from being the initial and dominant item, as the earlier investigators, including Hanot and Chauffard, supposed, must be regarded as the least essential of the three, and as the outcome of extension of the fibrotic process to the pancreas. In cases of bronzed diabetes which have been examined *post mortem* the pancreas has been found to be the seat of advanced fibrosis with copious deposition of pigment; whereas cases are met with in which there coexist cirrhosis of the liver and haemochromatosis, apart from glycosuria. In some such cases there have been found fibrotic changes in the pancreas also.

Hence the question resolves itself into that of the precedence of the two remaining events, cirrhosis of the liver and haemochromatosis, and we may either suppose that the haemochromatosis is the primary event, and that the deposition of the iron-containing pigment in the liver and pancreas gives rise to the fibrosis; or, again, that haemochromatosis results from a disturbance of iron metabolism brought about by the hepatic cirrhosis; or, lastly, that the cirrhosis and haemochromatosis are parallel effects of a common cause.

In support of the first of these theories may be adduced the fact, brought out by Gaskell and Vaile in their report on their histological examination, that wherever there was any considerable deposit of pigment, there also were some indications of fibrotic change. However, in the liver and pancreas the fibrosis was much more advanced than in other organs.

In many of the recorded cases of bronzed diabetes the habits of the patients



have justified the inference that the cirrhosis of the liver was the result of chronic alcoholism, and there are grounds for the belief that deposition of iron-containing pigment is, as Kretz maintains, a common feature in cases of cirrhosis. Further investigation along such lines, and especially of pigmentation of the skin in cases of cirrhosis, is to be desired. At any rate the association of cirrhosis of the liver with haemochromatosis would appear to be a very close one, and the few examples which have been placed on record of haemochromatosis apart from hepatic disease do not appear to me conclusive. If it can be shown that true haemochromatosis does actually occur in cases in which the liver exhibits *post mortem* no cirrhotic change, it will be necessary to abandon the theory that the cirrhosis is the primary event and the necessary antecedent of haemochromatosis, but neither of the alternative theories would gain in likelihood from the observation.

I must confess to a leaning towards the view taken by Potter and Milne, that what is called bronzed diabetes is not a disease *sui generis*, but rather the culmination of a series of events which are manifested to lesser degree in not a few cases of cirrhosis of the liver.

Perhaps the most helpful outcome of the work here placed on record is the evidence which is afforded that, in cases of haemochromatosis, the accumulation of iron in the tissues is not, like the deposits of iron in cases of haemolytic anaemia, due to any excessive destruction of blood corpuscles, but rather to a failure to excrete iron by the usual channels. The investigations confirm those of others who have failed to find evidence of undue haemolysis in cases of the same kind, and tend to support the view put forward by Parker that the iron set free in tissue catabolism fails to be got rid of, and so accumulates.

The evidence of such impairment of elimination is supplied by the chemical examination of the urine, bile, and faeces, and the absence of iron therefrom, in spite of the presence of some excess of iron in the blood. The fact that urine and bile are alike iron-free suggests that the failure to eliminate is due rather to the existence of the iron in a form not suitable for excretion than to defect of any special excreting organ. In other words, in haemochromatosis, as distinguished from haemolytic anaemias, we must assume a derangement of iron metabolism, and not an overtaxing of the eliminative functions. However, the histological examination of the kidneys, whilst supporting the view that there is a failure to eliminate the iron pigment, suggests a different interpretation of the facts. It will have been noticed that Gaskell and Vaile found the convoluted tubules of the first order free from pigmentation, whereas the glomeruli and tubules of the second order took the stain for iron—the latter especially. In haemolytic anaemia, on the other hand, iron is found in abundance in the tubules of the first order, and is almost confined to these; and this indicates a profound difference between the two conditions. Seeing that the appearances suggest that in haemochromatosis the iron is excreted by the glomeruli, and reabsorbed by the tubules of the second order, Gaskell is inclined to believe that the deposition of pigment in haemochromatosis is due rather to

peculiar avidity of the tissues for the iron compound than to a mere passive accumulation, resulting from an impaired excretion.

Although, as Mackenzie Wallis points out, a source of the accumulated iron might be looked for in the break-down of proteins other than haemoglobin, to me at least it does not appear necessary to look to such a source, in view of the normal haemolysis which must be constantly going on in the organism, and of the amount of which some rough measure is afforded by the daily output of bilirubin in the bile.

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## DESCRIPTION OF FIGURES.

PLATE 12. The appearance of the patient as he lay in bed in hospital.

PLATE 13, FIG. 1. Liver. Gelatin. Haemalum and eosin. Varicous lobules of liver cells, *l.c.*, are seen containing much pigment. The greatly increased fibrous tissue between these shows dilated portal veins, *p.v.*, and capillaries, *c.*; also 'pseudo bile-ducts', *p.s.*, and coarse pigment, *p.* The true bile-ducts, *b.d.*, especially when small, are also pigmented. The Kupffer cells, *k.*, also show coarse pigment.

FIG. 2. Kidney. Paraffin. Nishimura's method and alum-carmin. The greatly congested glomerulus, *g.*, shows iron pigment, *p.*, in its epithelial cells; the intertubular capillaries, *c.*, are also congested. The tubules of the first order, *t. 1*, show no pigment, but those of the second order, *t. 2*, are loaded with it.

FIG. 3. Pancreas. Gelatine. Haemalum and Sudan III. The greatly increased fibrous tissue, *f.t.*, is deeply pigmented. The parenchyma, *p.*, is strongly pigmented and often necrotic. An islet, *i.*, is seen lying against a vein, *v.*; it shows considerable pigmentation and also contains scattered fat. A normal duct, *d.*, is seen which is not pigmented.

PLATE 14, FIG. 4. Heart. Paraffin. Nishimura and alum-carmin. The muscle fibres, *m.f.*, are deeply pigmented; pigment, *p.*, is also seen free in a lymph space. Capillaries, *c.*, are congested.

FIG. 5. Thyroid. Paraffin. Nishimura and alum-carmin. The alveolar epithelium, *e.*, is deeply pigmented; the larger alveoli contain colloid, *c.*, in which lie pigmented cells and free pigment, *p.*

FIG. 6. Testis. Haemalum and Sudan III. Tubule, *t.*, is filled with fat. The vessel *v. 1* shows pigment in its endothelium; the smaller vessel, *v. 2*, shows, in addition, pigment in its wall. The interstitial cells, *i.*, contain both fat and pigment.





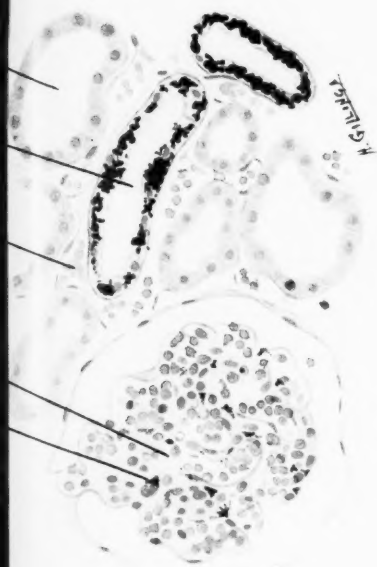


Fig. 2.

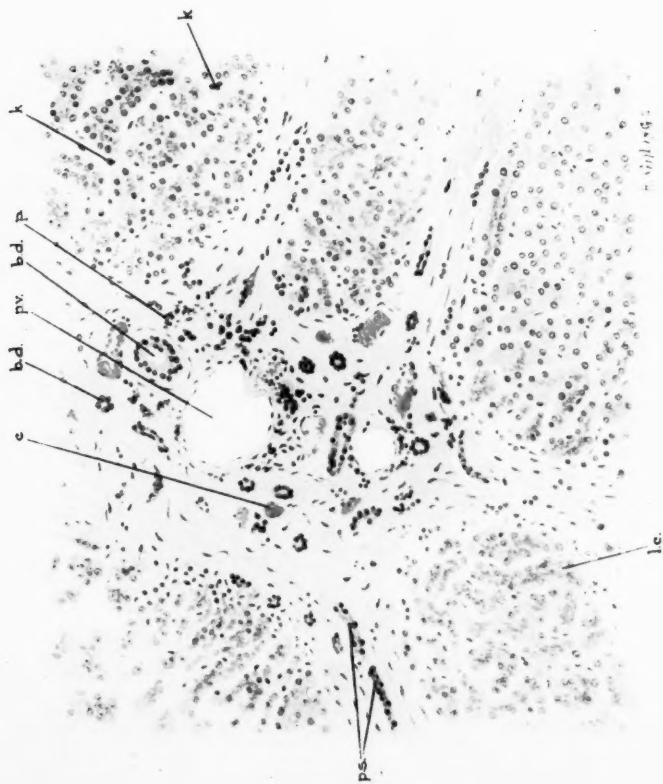
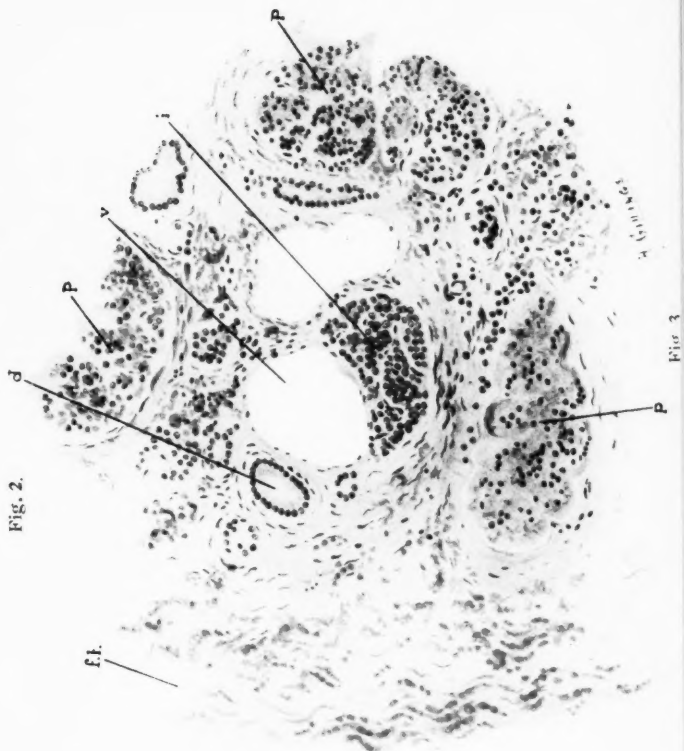


Fig. 1.







Fig. 4.



Fig. 5.

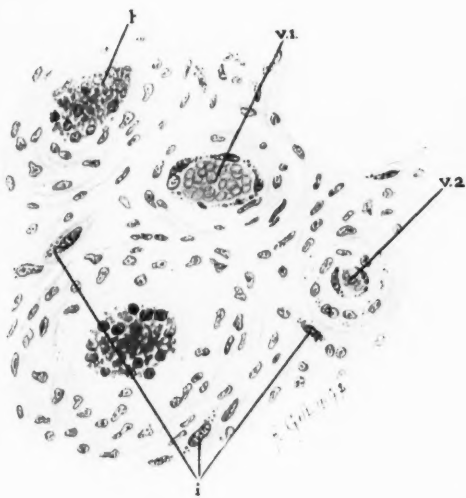


Fig. 6.



## ON THE INFECTIVE NATURE OF CERTAIN CASES OF SPLENOMEGALY AND BANTI'S DISEASE

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With Plates 15 and 16

MANY cases of enlargement of the spleen, with or without fibrosis, are met with both clinically and pathologically, the causes of which are unknown. Of the fibrosed spleens that are met with in the post-mortem room many no doubt cannot be further elucidated because the lesion is entirely healed, and unless there be evidence of other disease elsewhere, such as syphilis, tuberculosis, or malaria, it is useless to make even a guess. But in post-mortems of those cases belonging to the group of diseases which Osler has brought together under the term splenic anaemia, of which the terminal stage is Banti's disease, there might be some hope of determining a parasitic cause if such were present. Three considerations especially point to an infective origin of these cases: first, the fact that extirpation of the spleen cures or alleviates the condition; secondly, the similarity between kala-azar, especially that due to *Leishmania infantum*, and splenic anaemia; thirdly, the beneficial effects of such remedies as salvarsan. On general clinical and pathological grounds it is agreed that some haemolytic agent is produced in the spleen to account for the anaemia, and for the constant production of such a toxin we should at least exclude its production by an extraneous organism before attributing it to a perverted metabolism of the cells of the tissue where it is produced.

With these points in mind an exhaustive study was made of the organs of a case of Banti's disease which died in the Radcliffe Infirmary, Oxford, with the result that certain appearances have been discovered pointing strongly to an infection by a streptothrix organism. Similar appearances have since been found in five other spleens. Altogether, five of these six spleens are amongst the post-mortem material from the Radcliffe Infirmary, and occur in 300 consecutive post-mortem examinations—a proportion of 1.6 per cent. It will be convenient first to describe the features of the organs and tissues as ascertained *post mortem*, and then to describe in more detail the appearances suggestive of parasitic invasion.

*Description of Post-mortem Appearances.*

*Case I.* (P.M. 232.) Female, aged 37. During life the patient had splenomegaly, anaemia, and ascites, and was diagnosed as a case of Banti's disease.

*Post-mortem Notes.* The body was that of an extremely emaciated woman, aged 37. There was oedema of both feet. Three to four pints of clear ascitic fluid were found in the peritoneal cavity, and there was a marked increase of pericardial fluid. The right lung was adherent to the pleura.

The heart showed very marked subpericardial oedema. There was some thickening and calcification of the mitral valve and some oedema of the cardiac muscle, which looked gelatinous.

The oesophagus was normal. The thyroid was atrophied and yellowish on section. The glands of the neck were enlarged and showed early caseation, some showing earlier stage with discrete tubercle-like areas. The aorta showed early atheroma with one calcified patch.

Left lung: the surface was normal except at the apex of the upper lobe, where there was an old scar; on section it was oedematous. Right lung: old pleuritic adhesions, especially over lower lobe. On section of the lower lobe are a few raised reddish masses, not so large as a pin's head, suggesting the 'tubercles' seen in other organs.

*The spleen* was enormous,  $12 \times 7''$ ; the lower end reached to the pelvis and was turned on itself. On its outer surface the capsule was irregularly thickened. Some places showed small tubercular projections a little over a millimetre across, with larger similar projections in other parts. There were recent small infarcts here and there and a much larger one at the upper border of one of the notches. There was no calcification of veins. On the concave surface were numerous pigmented areas. On section the smell was peculiar; the surface was smooth, pale red, with trabeculae marked but not more numerous than normal.

Scattered here and there were small red areas not larger than a pin's head, and small irregular areas not more than 2 millimetres across, with branches of yellowish, hard but not calcified material. This stuff lay in the centre of some of the reddened areas and also in the substance of all the infarcts examined. In one or two spots the appearance suggested this to be a degeneration of a vessel and its contents. The spleen substance was extremely hard and cut with difficulty.

*Liver:* some perihepatitis was present over the anterior surface near the gall-bladder; nearly everywhere are to be seen minute pin-point whitish areas, subcapsular, similar to the areas described on the surface of the spleen, but in an earlier stage. On section the whole surface was peppered over with small raised whitish areas not bigger than a miliary tubercle, which they suggested. One of these areas, a little bigger than the rest, was bile-stained. In the left lobe was found a small yellowish area, the size of a pin's head, suggesting the areas described in the spleen. There was no increase of fibrous tissue to the naked eye, but the liver was as tough as the spleen.

Kidneys swollen, oedematous, fatty, with slight interstitial change.

Teeth bad and foul. Mesenteric glands slightly enlarged; those of the gastro-hepatic omentum were inflamed, one was undergoing caseation, another on section showed numbers of small white areas with indefinite margins.

There were some small ulcers in the caecum. In Douglas's pouch there was an implantation of numerous small tubercles with marked pigmentation and a projection from the uterus the size of a pea.

*Microscopically.* By ordinary methods of staining, there was fibrosis of the spleen and liver. In the latter organ there were numbers of miliary tubercles, in some of which tubercle bacilli were found. Tubercle bacilli were also found in the miliary tubercles in the lung. No tubercle bacilli could be detected in the spleen. The appearance of the spleen, after staining by Wheal and Chown's method, shows under low power black masses in the trabeculae in close proximity to the veins. These black masses in places can be seen to consist of threads and fibres of the type described more fully later.

*Case II.* (P.M. 208.) Male, aged 10½ years. Clinically, the patient had suffered from ascites and repeated haematemesis.

*Post-mortem Notes.* The body was that of a pale emaciated child with oedema of the scrotum. There were three small round cicatrices on the left leg below the knee.

The veins at the bottom of the oesophagus were very dilated and had a perforation at one spot; at another place there was ulceration over a vein. One vein in the stomach near the cardiac orifice was thrombosed. The aorta was normal. The heart was normal in size and as to cavities and valves; the muscle was very pale, but otherwise normal.

The lungs were normal externally; there was some oedema on section, and the bronchial glands were fleshy and anthracosed. The thyroid was normal; the tonsils were large, but normal on section.

In the abdomen were several pints of clear yellow fluid. The liver was small and very much puckered and misshapen by cicatricial contraction. Its upper surface was plastered over with firm, gelatinous, whitish material. On the anterior surface, close by the gall-bladder, there was very marked thickening of capsule. On section the appearance was one of multilobular cirrhosis, with more fibrous tissue in some parts than in others. This was true for the portion just beneath a thickening on anterior surface where the liver tissue was undergoing marked atrophy, the whole appearance being that of a chronic granuloma suggesting syphilis. The branch of the portal vein going to the thickening on the anterior surface had been recently thrombosed. A portion of the liver projecting from the under surface of the atrophied right lobe appeared on section to consist entirely of normal newly-formed liver substances. In the middle of this was a small area not more than ½ cm. across, with pale centre and a ring of hyperaemia round. The *spleen* was very greatly enlarged, about three times the normal size of an adult. The capsule was everywhere thickened, but on the

convexity more so than elsewhere. Here it was raised up into flattened tubercular masses as well as being generally thickened, and in places it was 3 or 4 mm. thick. It retained its shape and was very firm. Enlarged glands were present in the neighbourhood of the hilus. On section it cut firmly, showing a smooth surface in which the thickened trabeculae were everywhere prominent. The pulp was lightish red and the Malpighian corpuscles could easily be seen surrounded by a zone of darker red. The pulp could not be expressed. There was slightly more fibrous tissue around the veins which remained patent. Yellowish pigment could be seen in a few places, mostly in the neighbourhood of a vessel, and was surrounded by fibrous tissue. No recent thrombosis of vessels was noticed, but several places suggested that this had occurred.

The portal vein was very much dilated and the bile-duct was patent. Large numbers of haemolymph glands lay in the mesentery behind the peritoneum.

The duodenum and small and large intestines were normal. The stomach contained much recent clotted blood, but the mucous membrane was normal. The pancreas was pale and softer than normal.

The kidneys were pale and yellowish on section; no amyloid change could be detected. The surface vessels were firm and the medulla much increased. The testicles were normal.

The brain showed no change.

*Microscopically.* The spleen showed extensive fibrosis both generally and in the enlarged trabeculae; in the pigmented areas seen by the naked eye can be found the black threads around the veins described in a later section.

One section of the liver shows a necrotic area in which the limits of the liver cells are faintly discernible. There was slight round-cell accumulation, but no changes were detected in the vessels. The surrounding liver substance was healthy except for some fatty degeneration round the hepatic veins. A second section shows an enormously wide band of fibrous tissue with new-formed bile-ducts. Here there is more round-cell infiltration. No spirochaetes could be seen in sections of both areas when treated by Levaditi's method. A small artery in the kidney was obliterated by fibrosis.

*Summary and remarks.* The diagnosis of this case, both in the wards, at the post-mortem examination, and after a routine examination of the sections, was 'congenital syphilitic cirrhosis of the liver, ascites, recent gumma of the liver, syphilis of the spleen, hypertrophy of the medulla of the suprarenal'. It may be doubted here whether we are dealing with a single infection by the streptothrix found in the spleen, or whether syphilis is an added factor. It is to be noted that histologically the liver appearances give no positive evidence of syphilis and yet no streptothrix has been detected in the liver. It is interesting to note that on two occasions before death a Wassermann reaction had been returned as negative. Our methods of diagnosing syphilitic lesions in an organ are by no means as sure as, for instance, tuberculous lesions.



*Case III.* (P.M. 76.) Male, aged 11. Clinically, the patient had been intensely cyanosed, had undergone repeated tapplings for recurrent ascites, and had presented the usual features of chronic mediastino-pericarditis.

*Post-mortem Notes.*

Chronic adhesive pleurisy was present over the whole of the left lung; the right pleura was free; there was also chronic adhesive pericarditis and mediastinitis. The heart was small, the right side dilated, and the muscular tissue showed no obvious hypertrophy. The valves were normal. The left lung was small and firm, and showed no marked increase of fibrous tissue in the septa. Chronic stasis was marked. The right lung showed chronic stasis in all lobes. The bronchial glands of both lungs were enlarged and fleshy. The thyroid was hypertrophied.

In the abdomen there was recent general peritonitis, chiefly of the fibrous type, with an occasional bead of pus. The liver was enormously enlarged. The shape was roughly that of a normal liver with irregularities. One cicatricial depression was present on the under surface of the right lobe. There was slight roughening of capsule, and old chronic perihepatitis on the anterior surface, locally about one inch above gall-bladder. On section the surface was pale and smooth. Glisson's capsule was everywhere greatly thickened, and the blood content of the vessels was very evident. Fibrous tissue was irregularly deposited everywhere over the surface, giving the liver the appearance of multilobular cirrhosis. In some of the more fibrosed parts there was marked hypertrophy of the liver lobules. Fatty degeneration was everywhere present. Nowhere were granulomata seen. The gall-bladder was thick but normal. There was no evidence of thrombosis.

*The spleen* was the size of an adult, or slightly larger. There was a patchy thickening of the capsule on the convex surface. The organ retained its shape and was firm. On section colour was dark red; the pulp was firm, and could not be expressed. Numerous small trabeculae everywhere could be seen, as well as Malpighian bodies, which were small. The veins were patent and not thickened. Three spots seen with golden pigment were present. No thrombosis was present. The left suprarenal was normal, the right showed hypertrophy of the medullary tissue.

In the small intestine there were areas of small petechial haemorrhages; at two or three places were perforations which had set up peritonitis.

*Microscopically.* The lung showed coagulation of lymph in the alveoli and many catarrhal cells. The liver showed marked dilatation of capillaries, chiefly in the peripheral zone; there was marked increase of fibrous tissue and of the number of bile-ducts. Extreme fatty degeneration was present throughout. In the spleen the Malpighian bodies were prominent, the intervening tissue being engorged with blood, and there was evidence of chronic stasis. Stained by Wheal and Chown's method, the black-staining threads could be seen around the veins which showed pigmentation.

*Summary and remarks.* The diagnosis of this case was—chronic mediastino-pericarditis; enlargement of spleen; multilobular cirrhosis of the liver; ascites or stasis in liver, spleen, and kidneys; recent perforation of the small intestine. Syphilis was not suspected.

*Case IV.* (P.M. 295.) Male, aged 47. Clinically, the patient had chronic heart failure.

*Post-mortem Notes.*

The body showed marked oedema of the feet, legs, scrotum, and penis.

The lungs were everywhere adherent to the pleural cavity, adhesions being most marked on the left side. On section of both lungs several infarcts were present; these could be detected before section. Commencing gangrene was present in both lungs near the base; thrombosis of a branch of the pulmonary artery was found in association with each of these areas; old calcified glands were present at the roots of both lungs.

The heart was enormous, and weighed 26 oz. There was marked dilatation of all cavities, but the thickness of their walls was not increased, except in the case of the left ventricle. The aortic valves were thickened. The mitral and tricuspid valves were both thickened, but showed no recent vegetations. To the right of the interventricular septum, near the apex, was a large patch of organizing clot. The tricuspid valve admitted four fingers, the mitral three. Some atheromatous change was present at the base of the aorta, which increased markedly in the arch.

The liver was enlarged, hard, and had the features of chronic venous stasis. The kidneys were enlarged; the capsule stripped fairly easily, leaving several depressions, the results of healed infarcts. Several recent white infarcts were seen on section of both organs.

The suprarenals were normal. The spleen was not enlarged and was hard. The capsule was thickened with fibrous tissue, and on section the trabeculae were thickened and prominent. Stained by Wheal and Chown's method, a trabecula in one section showed the black-staining threads present in the former cases.

*Summary and remarks.* This was a case of chronic cardiac failure of unascertainable causation. The fibrotic condition of the spleen had no relation to the death of the patient.

*Case V.* (2749.) This was from a case of splenomegaly under the care of Dr. F. C. Purser, of Dublin, who kindly sent me a large portion of the spleen for examination.

The capsule was slightly opaque and thickened. On section the surface was firm and dark red. The trabeculae were not evident, and the Malpighian bodies could only be seen by a careful scrutiny. Several of the veins were thrombosed with red clot of recent origin. No infarcts were present, but small areas scattered over the surface of a section showed a much darker tint than the rest; these were not traceable to the thrombosis. A section stained by Wheal and

Chown's method has the appearance of a deeply stained red network, given as the second type in the description of the parasites.

*Case VI.* (P.M. 69.) Male, aged 48.

*Post-mortem Notes.*

The body was emaciated. Scars which suggested syphilis were present on the right tibia. There was no evidence of scarring on the penis. There was a recent operation wound in the right iliac region, in which was a drainage tube.

The left lung showed old pleurisy: there were numbers of tubercles in the septa and on the surface. On section scattered groups of tubercles in the early caseous stage were present over the greater part of the areas exposed. There was scarring at the apices of the upper and lower lobes. The bronchial glands showed tuberculous areas. The right lung was very adherent to the parietal pleura, and in removing the lung from the body a large cavity, with slightly roughened lining, was opened into the apex of the upper lobe. On section the upper lobe was infiltrated with small caseous areas at the apex, thickened and scarred in the neighbourhood of the cavity. A second smaller cavity was found on the external aspect of the upper lobe. The lower parts of this lobe and the other lobes showed scattered tubercles, as in the left lung.

On opening the larynx an ulcer was laid bare on the inner aspect of the left arytenoid; a beginning ulcer was found on the corresponding point of the right arytenoid. There was early tuberculous inflammation one quarter of an inch below the glottis in front. The glands at the bifurcation of the trachea were tuberculous.

In the heart there was old pericarditis, especially in front. The organ was flabby, not markedly enlarged, but the cavities were slightly larger than normal. There was old thickening of the mitral valve, otherwise the valves were normal. The muscle of the ventricles was flabby and brown.

The inner aspect of the aorta showed patchy atheroma; one spot was depressed and scar-like. There were enlarged fleshy glands in the mediastinum and mesentery.

*The spleen* was about twice normal size and of regular shape. There was evidence of slight perisplenitis in various parts, and the capsule was here and there raised into tubercular thickenings. On section the surface was darkened; the trabeculae were not well marked for the most part, the Malpighian bodies could be seen, and the pulp was more than normally firm. In two places there was an accumulation of gold-brown pigment not more than 4 mm. across; one of these was in relation to a trabecula, but the relation to the vessels could not be determined naked eye. In several places could be seen a small thrombosed vessel, and in other parts what appeared to be a fibrosed result of this thrombosis.

The liver was normal in size, and there were many recent adhesions between it and the neighbouring organs, especially the diaphragm. Scar-like depressions extended over the greater extent of the lower border and the neighbouring parts. On section there were scattered areas of fibrous tissue, but large sections were normal in appearance. On the right border was a small caseous granuloma

suggesting syphilis. The left kidney was normal. The right had a small cyst with clear contents in the lower pole. The capsule stripped fairly well.

The coils of intestines were everywhere adherent, the liver was adherent to the diaphragm, and the omentum was adherent in both iliac fossae. Pus and fibrin lay scattered everywhere. The posterior surface of the bladder showed peritonitis. The small intestine, including the duodenum, was normal except for the peritoneal coat. The appendix lay in a mass of connective tissue, and there was a perforation almost at its tip. The large intestine showed catarrh.

The testicles were normal.

*Microscopically.* The foci in the lung, apart from a few tubercles, showed an extensive necrotic centre surrounded by a layer of granulation tissue without the typical features of syphilis or tuberculosis. Tubercle bacilli could be found in all those examined as well as in the lining of the cavities. On staining by Wheal and Chown's method a brilliant red branching network is present as well. The granuloma in the liver had an increase of venules in its fibrous surroundings, but no endarteritis, obliterans, or giant cells were present, and no spirochaetes were seen in a section prepared by Levaditi's method. The spleen, stained by Wheal and Chown's method, showed parts in which the parasitic network was stained red, and parts also in which the black threads were more prominent, but in the latter case the structures were near a vessel.

*Summary and remarks.* The diagnosis made after the routine examination of the sections was: 'Chronic fibro-caseous tuberculosis of all lobes of both lungs with cavitation in the upper lobe of the left lung. Chronic perisplenitis. Perforation of appendix and acute general peritonitis. Old syphilitic scars on right tibia, and patchy cirrhosis of liver with a small gumma.' As in Case II, we have what appears to be a syphilitic element if the ordinary naked-eye features only of the liver are taken into account; as in that case it is better to suspend judgement, partly on account of the absence of specific proof of the spirochaete, and partly because, whether syphilis is present or not, the presence of another cause for the splenic condition is without doubt.

#### *Description of Parasites.*

In the spleens of all the cases enumerated can be found evidence of a parasitic invasion in such a relation to the tissue as to suggest its being the cause of the enlargement and fibrosis. They fall naturally into two groups, the first including Cases I-IV, the second comprising the fifth and sixth cases. The attempts to find a parasitic cause were made chiefly upon Case I. Numerous methods and many different stains were used without result; some of these will be mentioned later in so far as they enable us to exclude the appearances being due to tissue structures. The stain with which the possibility of a parasite becomes a certainty is Wheal and Chown's (1) method for staining clubs in actinomyces; briefly, it is a double stain, first by haemotoxylin, then by carbol

fuchsin, the decolorization being effected by equal parts of absolute alcohol and saturated watery picric acid.

A section of the spleen from Case I thus stained, looked at with the naked eye, appears a dirty green with some small black spots; these black spots are the areas surrounding certain of the splenic veins and correspond to the yellow pigmented parts seen in the fresh specimen.

Under the low power the area surrounding the vein, as well as the greater part of the vein itself, appears daubed and flecked with black; on closer inspection in certain areas these black parts consist of stems of various thickness down to the size of threads. Under the oil-immersion lens at a suitable place these last are distinctly seen; those lying in the plane of the section are long segmented threads varying greatly in thickness, but in those parts where the staining is deepest, where the growth is most active they are something under  $\frac{1}{2}\mu$  thick. Single threads can only be seen at the edges of the black masses; in the denser parts the threads are massed together into sheaves, some of which on cross-section show the individual fibres; others, however, partly perhaps because of the thickness of the section, show no differentiation into fibres; others, again, show a coarse fibrillar structure.

There is not much difficulty in separating the threads thus described, or the masses of them, from the tissue structures; in the walls of certain vessels, however, the distinction is not clear. Nuclei are stained a deep red, cytoplasm and fibrous tissue are stained yellow, and no other structure is the least like the blackness of the parasite masses.

The constancy with which the black-staining structures associate themselves with the vessels is a striking and characteristic feature of all the first four cases; the black substance in many sections is seen to invade the whole thickness and circumference of the wall in many cases up to the lumen, and to become so matted together that no thread-like constituents can be detected. Certain vessels are affected for a part only of their circumference. In the vessels themselves can be seen often a beginning thrombosis, usually peripheral, but in no instance yet seen has the black-staining substance penetrated into the lumen of the vein. In amongst the black masses are seen larger and smaller lumps of pigment varying in colour from a light brown to a yellow. From such an area, with its vessel in the centre, there radiates outwards thick strands of fibrous tissue connecting up with the other fibrous trabeculae. Often, too, where the black substance is small in amount and limited to the immediate surrounding of the vein, the fibrous tissue is very abundant and thick, and, conversely, where the black substance is large in amount the fibrous tissue is not so abundant, indicating possibly a healing tendency in the former. The infarcts are always associated with a vessel thus affected near the apex of the infarcted area. Many of the veins which show none of the black staining are nevertheless thickly coated with fibrous tissue, indicating that the healing processes have removed the parasite.

The appearances thus described suggest at once that some tissue structure



may have taken on the black stain and has simulated a parasite. It is not fibrin, for it does not stain with Weigert's fibrin stain, when fibrin can readily be seen in some of the venules. It is not fibrous tissue, for with van Gieson's stain it remains yellow. It remains unstained by Weigert's elastic tissue stain; it is Gram-negative, and not acid-fast. Haematoxylin stains it very faintly, and all other stains tried have no affinity for it. The thicker masses, but not the finer threads, give a definite reaction for iron.

It remains now to describe the different phases that can be noticed by a careful search amongst the parts where the threads are less densely packed. The threads in certain parts are obviously undergoing segmentation, as can be seen by a clear line across the fibre (Pl. 16, Fig. 3). In other places the segmentation is into shorter rods of an ordinary bacillary form with rounded ends, such bacillary forms being separated completely from the parent thread; these appearances are found at the edges of the masses when the threads are invading the surrounding tissues.

Some of the thicker threads are undergoing a hyaline change and are being segmented into granules with a very high refractive index. As soon as they assume this hyaline appearance they begin to lose the property of taking on the black stain. There seems to be a transition between these groups of small granules, which may sometimes be seen in threads, and the larger pigment granules and lumps, but the transition cannot be traced with certainty. The thick bundles of fibres are occasionally seen to become less dense, and the constituent thread to become very attenuated and granular.

In the same organ, often in the same section, can be seen long thin unbranched fibres, and thicker fibres with branches in a tree-like fashion, the branches bending in various directions like those of an oak growing in the open.

The second type of parasite, that seen in Cases V and II, cannot be detected by the naked eye either in the stained or the unstained sections. This again stains best by means of Wheal and Chown's stain, but takes the fuchsin stain, the haematoxylin fixing itself to portions only, and that slightly. On looking at a section of any part of the spleen under the low power a very little search will enable a fine mycelium-like network of brilliant red colour to be seen. These masses, which are roughly circular or oval, lie in the clearer non-cellular part of the splenic pulp where there are many red blood-cells; in fact, its discovery is facilitated very considerably by confining the attention to the clearer parts. No other structure takes on the fuchsin stain in this intense fashion, unless perhaps the section has not been sufficiently washed in picric acid alcohol, in which case the red blood-cells may approach the same tint. Under the oil-immersion lens irregular masses of a fuchsin-staining substance are to be seen, some parts staining a much deeper tint and being slightly more hyaline than the rest. From these masses, which occupy only a small part of the area concerned, there stretch out in all directions an irregular loose felt-work of branches and threads.

The thickness of the threads varies at every point, and each fibre branches and rejoins the neighbouring fibres, at frequent intervals surrounding such splenic



cells and blood-cells as happen to be implicated, the whole suggesting a very tangled piece of wire-netting, of which the wires are of very uneven thickness. The thicker parts of the threads are stained darker and appear more hyaline than the thinner parts. Some of the branches end in slightly bulbous extremities, shaped like an Indian club (Pl. 16, Fig. 5). In certain parts, spore-like bodies are to be seen entirely cut off from the network; some of these are like cocci, others much larger, round or oval; others, again, are thick, short bacilli, and others curved with projections upon them, but all stain very deeply with the fuchsin and are very hyaline. Their manner of production appears to be due to the disappearance of the lighter parts of the threads and branches, leaving only the more deeply stained portions, which become rounded off where they joined the thread. In one section a portion of the branch-work was found which stained somewhat with haematoxylin, but the details could not be so easily made out, and the structures appeared to be degenerate. The network of threads is for the most part Gram-positive (Claudius's modification). The network is not fibrin, for though it stains with Wiegert's fibrin stain, being Gram-positive, fibrin in vessels in the same section does not take on the fuchsin stain by Wheal and Chown's method such as this structure does. It is not fibrous tissue, because it remains unstained by van Gieson's stain. It is not elastic tissue, for it remains unstained by Wiegert's elastic stain. It is not acid-fast to carbol-fuchsin.

Unfortunately no cultural proof is yet available that these structures are parasites. Only in one case (Case I) were cultures made of the splenic pulp. This was, however, before any evidence of a parasitic invasion was to hand, and the media used were those in ordinary laboratory use, viz. agar and blood agar, upon which nothing definite grew during the time the tubes were incubated. All the other spleens had been preserved by Kaiserling's method for some time previous to their being examined.

#### *Conclusions.*

In the spleen of six cases, three with the picture of Banti's disease, two with splenic enlargement and fibrosis, and one with splenomegaly, there can be found, by a special method of staining, an appearance which can be interpreted only as a parasitic invasion of the organ by a streptothrix organism, this being in such a relation to the affected parts, at least in the cases of Banti's disease, as to leave no doubt that they are the cause of the pathological condition. Many other spleens examined with the same object in view, several of which had pigmented spots, showed no such appearances.

Two different appearances are described, one being present in four cases, the other in two, which at first sight suggest two different species of streptothrix. Such differentiation must be left unsettled, for it has yet to be determined how far these appearances are due to different stages or variations in growth or to degeneration forms; for in the spleen of Case VI some parts of the parasite take the red stain and others the black.

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## DESCRIPTION OF PLATES.

PLATE 15, FIG. 1. Microphotograph of a section of one of the splenic trabeculae (Case I) in which could be seen, naked eye, the yellow pigment stained by Wheal and Chown's method ( $\times 80$ ). Notice the black masses in the fibrous tissue of the trabecula and in close proximity to the vessels.

FIG. 2. Microphotograph showing the threads at the edges of the black masses. The nuclei are seen as round or oval black areas.

PLATE 16, FIG. 3. (Case I.) Showing the black threads under a high magnification. Notice the septa in some threads and the segmentation of others (Wheal and Chown's stain).

FIG. 4. (Case VI.) Showing the thicker branch-work (Wheal and Chown's method).

FIG. 5. (Case V.) Showing the network in the second type stained by Gram's method (Claudius's modification). One club-shaped extremity is to be seen.

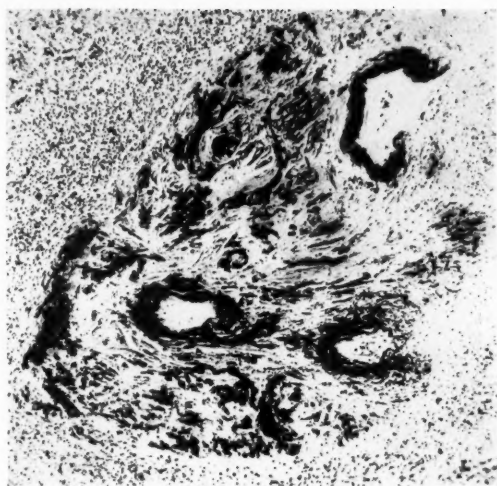


FIG. 1

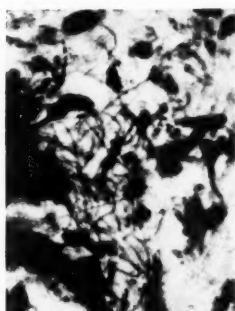


FIG. 2





Fig. 3.

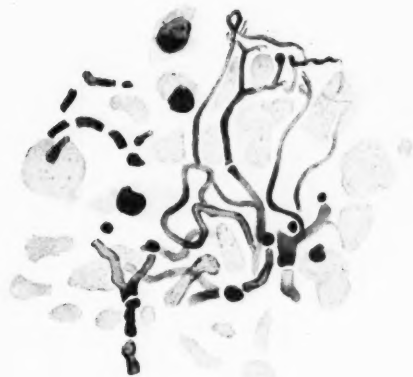


Fig. 4.

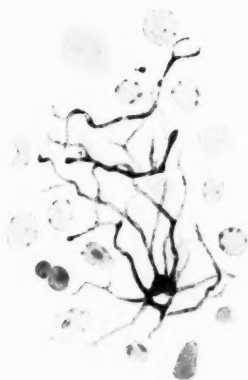


Fig. 5.





*Phys. analysis*

## ON PNEUMO-PERICARDIUM

By JOHN COWAN, ARCH. W. HARRINGTON, AND J. R. RIDDELL

With Plates 17 and 18

THE case of pneumo-pericardium which we report below is interesting for several reasons. Pneumo-pericardium is apparently extremely uncommon, and we have only been able to discover forty-three cases in the literature, thirty-eight of which are collated in James's valuable paper, from which we have quoted in considerable detail. In only four of these cases was the pneumo-pericardium unaccompanied by pericarditis, and the signs which are considered to be *characteristic* of pneumo-pericardium are really those of hydro- or pyo-pneumo-pericardium. In our case, from some unexplained reason, the signs were not typical, inasmuch as the apex-impulse and the area of cardiac dullness did not disappear, and the diagnosis was only made on X-ray examination. The skiagrams are almost unique, as only one has hitherto been published, that of Wenckebach's case, in which pneumo-pericardium was induced to assist the absorption of a large chronic tuberculous effusion.

A boy, aged 8, was admitted into hospital on October 2, 1912, on account of sickness and vomiting of four days' duration.

He had always been a healthy boy, save for an attack of measles in infancy, and had seemed in good health on September 28. Next morning he felt sick and vomited, and his mother kept him in bed. The vomiting recurred and he became fevered, was restless, and rambled in his talk. The symptoms persisted, and on October 1 headache was complained of, and he frequently put up his hands to his occiput.

On admission he was mildly delirious and very restless, and constantly moved his limbs in an erratic way. He often placed his hands at the back of his head. The skin was pale, dry, and harsh. The face was flushed, and the conjunctivae were inflamed. He took his drinks well, but passed both urine and faeces in bed. There were few objective signs. There was a slight catarrh in the chest. The cardiac dullness was normal and the sounds were pure; no friction was heard. The tongue was dry and brown. The left membrana tympani showed some old cicatrices, and the right a large chronic perforation from which issued a very small quantity of slightly odorous muco-pus; but there was no mastoid tenderness, and no palsy, spasm, or inequality of reflex could be discovered, save that the right pupil was slightly larger than the left. Kernig's sign was negative. During the succeeding week slight improvement ensued, the delirium becoming less and the pulse-rate diminishing in frequency. On October 5, however, the stools contained a considerable amount of muco-pus, which persisted for twelve days. The pupillary inequality was inconstant. Râles were now audible at the bases of the lungs. On October 14 he

suddenly became extremely livid and very ill, and appeared to suffer abdominal pain. On October 17 the abdomen was for the first time somewhat distended, and a small consolidation was recognized at the base of the right lung. On the 20th new physical signs were recognized on the front of the chest. The percussion note at the left apex was skodaic in character, and an area of dullness ran outwards from the heart to the left shoulder; the respiratory murmur was very deficient. The area of cardiac dullness was increased in every direction, but the sounds were normal (Fig. 1). The signs at the right base were unaltered. Little change was noticed during the next few days, but the dull area on the front of the chest had disappeared on the 26th, though the respiratory murmur at the left apex was still very deficient.

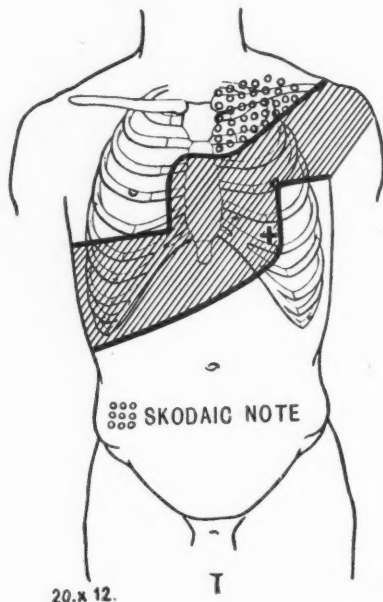


FIG. 1. The physical signs on Oct. 20, 1912.

His general condition slowly improved, though the fever still persisted. On November 12 the chest was carefully examined and the area of tympanitic percussion, shown in Fig. 2, was now recognized. It may have been present for a few days previously, as the chest was not examined on every day. The apex impulse persisted in the fifth interspace just within the nipple line. The consolidation at the right base was larger than it had been. Progress thereafter was continuous though slow. The physical signs gradually cleared up, and on December 6 the front of the chest seemed normal. The liver was still enlarged and the basal consolidation was resolving. On dismissal on January 19, 1913, he was fat and well, though the pulse-rate was still rather frequent. In June, 1913, he was very well and attending school regularly. There was still some dullness on percussion and deficiency of the respiratory murmur at the right base.

During his residence in hospital the fever was slight and only exceeded 100° F. on October 19, 20, and 22, reaching a maximum of 100.8° on the latter date. It never rose above 99° after December 16. The pulse-rate rose to

156 on October 3, but fell to about 125 three days later, at which rate it continued until the second week of December, when it tended to run at lower levels, but it was still in the neighbourhood of 100 on dismissal. The respirations numbered 44 on October 5 and thereafter ran about 30, falling to normal limits in the middle of December.

The case presented many interesting features, and an accurate diagnosis of the sequence of events is impossible. On admission the symptoms suggested the presence of meningitis, but no source of infection was discovered; the aural sepsis seemed quiescent. The Widal test, &c., were all negative, no

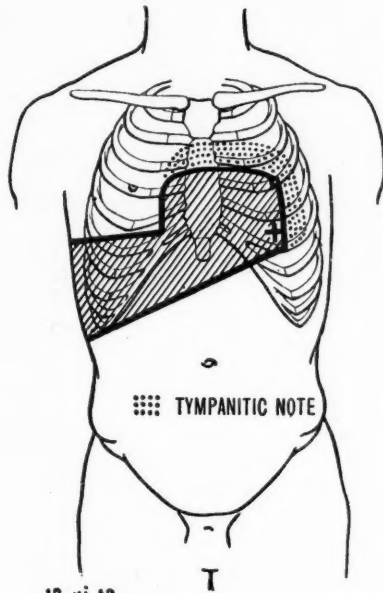


FIG. 2. The physical signs on Nov. 12, 1912.

sputum could be obtained, and a septicaemia of unknown nature was the only diagnosis. The cause of the exacerbation of the symptoms on October 14 was not recognized, and the pneumonia was only apparent three days later. The interpretation of the new physical signs on October 20 was also difficult, and it was only on October 28 that his general condition permitted examination by the X-rays, and the pneumo-pericardium was recognized. The skiagrams are instructive. On October 28 the distension of the pericardium is probably uniform, the heart is but little displaced, and the pneumonia is evident (Plate 17, Fig. 1). On November 11 the distension of the sac is considerably larger, but only towards the left side and immediately below the apex, and the heart is *displaced* towards the right (Plate 17, Fig. 2). On November 22 the heart seems still displaced, but the gas is in less amount and almost wholly on the left side (Plate 18, Fig. 3). On December 6 the distension is less and the heart has

returned to its normal site (Plate 18, Fig. 4). On December 16 the distension was less, and subsequent skiagrams failed to reveal any evidence of gas in the pericardial sac. The distension of the pericardial sac was never quite uniform, for the apex impulse persisted throughout, and the area of cardiac dullness also remained, so that the heart can never have left the front of the chest. There was at no time any evidence of pericarditis, and there was no history of any illness in the past likely to produce pericardial adhesion, so that the cause of the localization of the gas is unknown.

It seems possible that the original septicaemia provoked (or originated in) a local lesion of the mediastinal glands, which on October 14 became disseminated more widely, involving first of all the right lung and subsequently the pericardium, and permitting the entrance of air into the pericardium from the lung. The possibility of a gas-producing infection of the pericardium seems slight, for at no time was pericardial friction observed, and the skiagrams exclude the presence of an effusion.

The only skiagram which we can discover in the literature is that which was taken in Wenckebach's case. It differs in some respects from Plate 17, Figs. 1 and 2, Plate 18, Figs. 3 and 4. The heart appears to be in its usual situation and is not displaced. The pericardial sac is uniformly distended and projects well to the right of the right auricle. The upper margin (as in Plate 18, Fig. 3) extends higher upon the left side of the chest than upon the right. The lower border and the apex impulse are not defined, as the heart in this situation dipped into the fluid effusion in the lower recesses of the sac.

In a case recorded by Ljungdahl the diagnosis was made by the X-rays, but no skiagram was taken. The patient was a man, aged 18 years, who was suddenly seized with severe pain in the chest. On examination the apex impulse and the area of cardiac dullness were normal, and pericardial friction was audible. On the next day the area of dullness had disappeared and the percussion sound was tympanitic. X-ray examination showed a dark line to the left of the cardiac shadow, from which it was separated by a light band about 1 cm. broad. The patient made a good recovery.

The presence of gas within the pericardial sac is apparently of very rare occurrence, for James, when recording his case in 1904, was only able to find thirty-seven undoubted cases in the literature. To these we can only add the cases recorded by Ljungdahl, G. A. Gibson, Kerr Love, Lundie, and Sorauer, and that which is recorded above. It seems probable, too, that these figures represent the real incidence, for the physical signs are so striking that they are unlikely to escape observation.

Pneumo-pericardium may conceivably arise in several ways. In thirty-four cases there was an accidental communication between the sac and some other viscus; in eight, as in our own case, no communication was apparent. The absence of an obvious cause suggests that the gas may have arisen from infection by one of the gas-producing organisms, but as yet no such

case has been recorded, though the known occurrence of pneumo-thorax from this cause suggests the possibility of pneumo-pericardium originating in the same way.

In a large number of cases the pneumo-pericardium was due to the entrance of air through a wound. In nine cases the pericardium was punctured from without, and in two through the oesophagus, in one case during a sword-swallowing performance. In seven cases no external wound was found, but the lesion followed a trauma of the chest which presumably occasioned rupture of the pericardium and of the lung, and allowed the entrance of the pulmonary air into the sac. The case recorded by Gibson occurred during paracentesis of the pleural cavity.

In another group ulcerative processes permitted the entrance of air. In five cases the oesophagus was primarily involved (in three cases by cancer). In four cases the softening of a tuberculous focus in the lung or lymphatic glands established a fistulous communication between the pericardium and the lung or the oesophagus. In four cases the primary lesion was beneath the diaphragm (hepatic abscess, appendicitis, gastric ulcer (two)). In four cases the primary lesion was pulmonary (empyema, pneumo-thorax, pneumonia followed by gangrene). In Stokes's and Ljungdahl's cases the primary lesion was pericarditis.

In the majority of cases the lesion which occasions the pneumo-pericardium permits, in addition, an infection of the sac, and an effusion, which is commonly purulent, sooner or later develops. The symptoms and physical signs are in consequence due in part to the pericarditis, and in part to the presence of air within the sac.

The onset of the *symptoms* may be gradual or sudden. In the former case the symptoms are those of acute pericarditis. In the latter the *sudden* occurrence of cyanosis, collapse, syncope, praecordial oppression or pain denote the advent of the new lesion.

The *physical signs* are striking, and led to a correct diagnosis during life in thirty-six cases. The apex impulse disappears, though it has been observed to return if the patient assumed the prone position. The area of cardiac dullness disappears and is replaced by an area with a tympanitic or a skodaic note. In Stokes's case a *bruit de pot fêlé* was present for a time. As effusion develops, the area of tympanitic percussion sound becomes diminished and varies in site according to the position of the patient. This was very apparent in James's case. The auscultatory phenomena at this stage are characteristic, the cardiac contractions producing the rhythmic churning, splashing 'mill-wheel' sounds, which are distinctive of the presence of air and fluid within the pericardium. Metallic tinkling has often been noticed. Friction sounds of the usual kind generally coexist.

Stokes (7) described the auscultatory phenomena as follows :

'On examination a series of sounds was observable which I had never before met with. It is difficult or impossible to convey in words any idea of

the extraordinary phenomena then presented. They were not the rasping sounds of indurated lymph or the leather creak of Collin, nor those proceeding from pericarditis with valvular murmur, but a mixture of the various attrition murmurs with a large crepitating and a gurgling sound, while to all three phenomena was added a distinct metallic character.'

James's description is more detailed :

'When the patient takes a full breath and holds it there is heard by the listening ear, held twelve inches from the chest-wall, a peculiar clicking sound synchronous with the cardiac systole; this click has a musical quality with the quality of a succussion sound or splash. It disappears with extreme expiration. Upon applying the ear or stethoscope to the precordium the heart-sounds themselves are dull and muffled, but there are heard certain remarkable and unusual phenomena. The first sound is accompanied by a loud metallic tinkle of splashing, gurgling quality suggesting the sound made by an old-fashioned over-shot water-wheel—the *bruit de la roue hydraulique*. It is as if a very marked succussion were brought out by each systolic contraction of the heart, together with many metallic tinkles. This sound is heard loudest in the third, fourth, and fifth left spaces and in the third and fourth right spaces. . . . It is heard loudest during inspiration, rather less during expiration. Its intensity varies from time to time without apparent reason.

'The foregoing signs are obtained while the patient lies upon her back. When lying on the right side there is heard in the precordium between the middle line and the left nipple a typical to-and-fro pericardial friction sound, superficial, sharp, and clear. In this position the splashing succussion sound and the metallic tinkle are not heard. When the patient lies upon the face or rests upon the elbow and knees the signs are the same as when lying upon the right side.'

The *prognosis* is better than might be anticipated, for fifteen out of forty-three cases recovered. In many of the fatal cases, too, the primary lesion was sufficient to cause death.

The *treatment* of pneumo-pericardium must be conducted upon ordinary lines. Pyo-pneumo-pericardium suggests the advisability of surgical interference if the general condition of the patient permits. In James's case, which was due to perforation of the oesophagus by a small spicule of a mutton-bone, death followed twenty-two hours after the operation.



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## DESCRIPTION OF FIGURES.

PLATE 17, FIG. 1. Skiagram on October 28, 1912. The heart is in its normal situation. A consolidation is apparent at the right base. The pericardial sac is distended with gas.

FIG. 2. Skiagram on November 11, 1912. The heart is displaced to the right side. The pulmonary consolidation is larger. The distension of the pericardial sac is much greater than on October 28 and is localized.

PLATE 18, FIG. 3. Skiagram on Nov. 22, 1912. The distension of the pericardial sac is lessening.

FIG. 4. Skiagram on December 6, 1912. The heart has regained its normal situation. The distension of the pericardial sac is lessening.





FIG. 1



FIG. 2



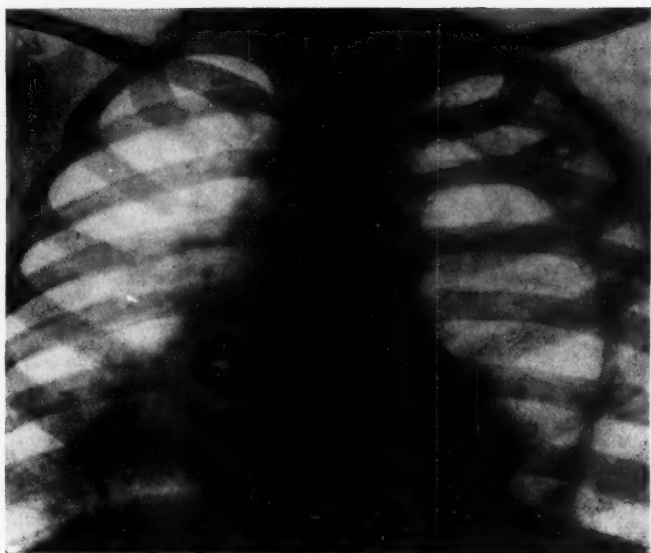


FIG. 3

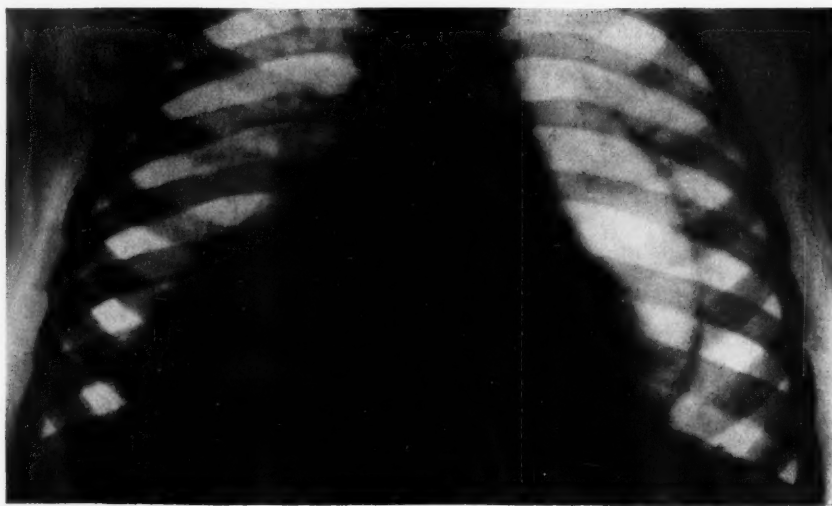


FIG. 4





## CRITICAL REVIEW: THE PITUITARY BODY

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### *Introduction.*

SINCE Marie, in 1886, first drew attention to the symptom complex of acromegaly and its association with functional changes in the hypophysis, the latter organ has become the subject of serious thought and investigation and a great deal of speculation, and recently all the more so on account of the renewed and active interest in the glands of internal secretion. Many have been the publications since the report of this distinguished French investigator, so that at the present time the bibliography has grown to such an extent that the individual reports upon the subject of the hypophysis number into the hundreds. It is of course impossible to give all of these reports the space which they deserve, consequently in this review I shall attempt to give a general oversight of the whole subject and draw especial attention to the various phases of the work as they have been presented. The results of the various investigations will not be discussed, except in a few instances, in the sense of a critical review; on the other hand, the more important work will be cited chronologically as far as possible, and the development of our ideas and knowledge pertaining to the hypophysis will be indicated by the contributions which in the most part have been distinct advances, as later investigations have shown. Finally, I hope I may be pardoned if in regard to recent work and theories I report in greater detail results of investigations carried on in the laboratory and clinic with which I have been associated.

### *Embryological Development.*

The pituitary body was regarded by the ancients as a glandular structure which discharged a mucous secretion (*pituita*, mucus) into the nostrils. The term 'hypophysis cerebri' was first applied by Soemmering in 1778. The two terms are now used synonymously. The hypophysis consists of two genetically entirely different portions, a larger anterior, glandular, epithelial portion, called the anterior lobe, or the 'pars anterior', and a smaller posterior or nervous lobe, 'pars nervosa', or infundibular portion, composed of nervous tissue, the whole connected with the floor of the third ventricle of the brain by means of the stalk

or infundibulum. A further subdivision is made of the epithelial portion into the 'pars intermedia', called also the intermediate lobe or the epithelial investment of the posterior lobe, which almost completely surrounds the pars nervosa and sends off epithelial cells into it. The hypophysis is found in this form in mammals, birds, and bony fishes. The pars intermedia is separated from the pars anterior by a cleft, the residual lumen of the ectodermal invagination from the pharynx, to be described.

The anterior lobe is developed—in man in the fourth week—from an ectodermal pouch which evaginates from the roof of the bucco-pharyngeal cavity in the direction of the mid-brain, and is called, from the name of the man who first described it, Rathke's (1838) (69) pouch. This process was later described in greater detail by Mihalkowicz (1875) (59). Rathke believed that the epithelial portion of the hypophysis was derived from this pharyngeal invagination, but that it was of entodermal origin. Müller (1871) (61) also demonstrated that the anterior lobe is derived from Rathke's pouch, but believed similarly that it was of entodermal origin. Later researches show that the pouch is derived from the epithelium of the buccal cavity immediately in front of the oral plate. By the subsequent growth and formation of the sphenoid bone the cavity of Rathke's pouch becomes constricted off and obliterated, with the exception of the tip, which remains as the cleft in the adult gland, a line of cleavage between the thinner, less differentiated, posterior portion of the hypophysial vesicle and the thicker, more highly specialized and differentiated anterior lobe. This posterior surface, which develops into the pars intermedia, applies itself to a down-growth of nervous tissue from the mid-brain or third ventricle, called the infundibulum, which becomes the stalk of the pituitary body. This process gives rise to the posterior or nervous portion of the hypophysis. The term 'posterior lobe', in later investigations, has come to mean the true nervous portion of the gland, together with its epithelial investment. The original canal connecting the hypophysial vesicle with the pharynx becomes constricted off and remains as a solid strand of cells connecting with the pharyngeal epithelium, in which it is gradually lost. It was formerly the opinion of most observers that these embryonic remnants or 'rests' of the original Rathke's pouch and its pharyngeal connexion became entirely obliterated and were never to be considered again. The excellent work of Erdheim, Harujiro Arai, and Habersfeld has demonstrated to us, however, that embryonic 'rests' are frequently found in the adult along the path of ascent of the hypophysis from the pharynx to its final resting-place in the sella turcica. Erdheim (1904) (23) was the first to emphasize the fact that it is not at all uncommon to find near the hypophysial cleft, and applied to the infundibulum, inclusions of squamous, epithelial cells, or even ciliated cells in groups, which represent presumably 'rests' of the primitive ectoderm of Rathke's pouch, and which undoubtedly give rise to certain epithelial growths and cysts which are frequently found in this region: a further consideration of this will be given in the discussion of the pathology of the hypophysis. Erdheim drew attention also to the occurrence of hypophysial tissue in the pharyngeal vault in

a number of foetuses and new-born infants. This tissue was regarded as a remnant of the pharyngeal end of the canal connecting with Rathke's pouch and was called by him the 'Rachendachhypophyse'. The latter was also described by Harujiro Arai (1907) (41) under the name of 'Hypophysis accessoria pharyngea'. Occasionally a bony canal persists in the body of the sphenoid and connects the pharyngeal hypophysis with the floor of the sella turcica. The term 'canalis craniopharyngeus' has been applied to it. Here and there embryonic remnants are sometimes found in this canal in the body of the sphenoid bone. These findings stimulated Haberfeld (1909) (39) to a very thorough study of the subject in a series of foetuses, new-born children, adults, and in the aged. His findings were very striking and interesting. He showed that in a careful search of the pharyngeal vault, without regard to age or sex, there was to be found, without exception, a cell cord with a connective-tissue envelope and consisting of cellular elements identical with those of the anterior lobe of the hypophysis. The length of this gland varied according to the age from 1 to 7 mm., and from 1/5 to 1 mm. in width and thickness. On account of the constancy of this tissue and its similarity in structure to the anterior lobe of the hypophysis he felt that it should be considered as an independent structure with a distinct function of its own, and therefore suggested for it the name 'hypophysis pharyngea'. This finding is important not only for pathology, but also for physiology, for it becomes at once evident that in speaking of the effects of total removal of the hypophysis one must always think of a possible compensatory action of this glandular structure as well as of other embryonic 'rests' mentioned.

One of the greatest difficulties which has stood in the way of investigations on the hypophysis has been its inaccessibility. It lies in the most protected spot in the skull, encased in the bony sella turcica and in the anterior angle of the optic chiasm. A firm fibrous connective-tissue layer, the diaphragma sellae, a part of the dura mater, separates it from the cranial cavity and allows only the passage of the pituitary stalk or infundibulum through a perforation in its middle. The normal hypophysis varies very much in size and weight. After birth it gradually increases in size and reaches its maximum between the thirtieth and fortieth year of life. According to Schönemann (1892) (78), its average weight is 0.59 grm.

#### *Normal and Pathological Anatomy.*

Creutzfeldt (1909) (11) presented an excellent summary of the normal and pathological anatomy of the human hypophysis, from which I have in part drawn in considering this phase of pituitary work. The anterior or glandular part of the hypophysis is considerably larger than the posterior or nervous part, and gives the gland its characteristic pinkish-grey appearance in its fresh condition. The anterior epithelial part is further divided into the large 'pars anterior' proper, which constitutes about three-fourths of the gland and presents

the typical pinkish-grey appearance (Peremeschko's Korkschieht, 1867) (66), and the posterior narrower zone of whitish appearance (weisse Markschieht—Peremeschko), called also 'pars intermedia'. The latter constitutes the epithelial lining or investment of the posterior lobe, and runs up the infundibulum frequently even to the floor of the third ventricle. Between these two divisions of the epithelial or glandular portion lies the cleft, the embryonic remains of the original cavity of Rathke's pouch, which often contains a colloid and sometimes a granular substance and is lined frequently with ciliated cells. Müller (1871) (62) described the hypophysis as consisting of tubular cords of cells which branch and form alveoli composed of cylindrical cells at the periphery and polygonal cells at the centre. The alveoli are in places filled with cells, in other places with colloid. He did not distinguish the cells by their staining qualities. He speaks of the occurrence of colloid in the posterior part of the anterior lobe, meaning thereby in all probability the pars intermedia. Flesch (1885) (28) was the first to point out that there were two fundamentally different types of cells in the anterior lobe depending upon the affinity for stains—the chromophilic, which stained intensely in either the acid or basic stains, and the chromophobe, which remained unstained. He found that the chromophil cells possessed an abundant protoplasm rich in granules which have a marked affinity for stains, whereas the chromophobe or chief cells possessed little protoplasm, were less clearly differentiated, were stained with difficulty, and were non-granular. Rogowitsch (1888) (72) described a third kind of cell occurring in the anterior lobe, which he called 'Kernhaufen'. He regarded the latter as a kind of embryonic tissue, characterized by groups of nuclei without cell boundaries and with practically no protoplasm. Stieda (1890) (80) agreed with Rogowitsch as regards these peculiar cell groups, but regarded them as chromophobe chief cells with a scanty non-stainable protoplasm. Schönemann (1892) (78) described an epithelial arrangement of the chromophils around a central lumen, which frequently contained 'colloid', with nuclei and nuclear fragments. He suggested that the formation of this colloid, frequently seen in the anterior lobe, occurred in the cell protoplasm at the expense of the latter, and states that it was also found in the blood-vessels and vascular spaces. In the vicarious hypertrophy of the hypophysis after thyroidectomy he found an increase in the chromophil elements. Thom (1901) (83) believed that the secretion of the chromophil cells, represented by the granules, mixed with the thinner secretion of the chromophobe cells, and then in combination with the latter diffused through the membrana propria of the alveoli to enter the interfollicular lymph spaces. Benda (1900) (2), similarly to Rogowitsch, distinguished three types of cells, but could not confirm the findings of the latter in regard to the 'Kernhaufen' or nuclear accumulations. Benda distinguishes—

1. The small, ill-defined, pale cells with a slight acidophilic and some basophilic protoplasm: these he regards as young forms;
2. The larger, sharply defined, acidophil or eosinophil cells, which are most numerous near the centre of the anterior lobe; and

3. The largest cyanophil cells, which are faintly basophilic or amphophilic, he regards as adult cells, the granules having disappeared by lysis.

Benda believes that these different types of cells represent different secretory or functional stages of the same fundamental cells. He regards the small, irregular, cylindrical, non-granular chromophobe cells as in the first stage of functional activity, the larger mono- or multinuclear acidophilic granular cells as at the height of activity, and the large, pale, non-granular cyanophilic cells he looks upon as discharged eosinophilic cells in the last stage of activity. Benda further regards the number of acidophilic granules as an index to the activity of the cell, and the granules themselves as the real glandular secretion. This view seems a very simple and plausible one. In the writer's own experience there has been no difficulty in demonstrating these different types of cells as described by Benda, and the shades of variation between the types are so numerous that a series of very gradual gradations can easily be picked out; thus it would not seem to be presumptuous to think of one type changing into that of its neighbour. Cells with both basophilic and acidophilic granules side by side in the protoplasmic body are not uncommon, and the classification of these cells depends merely upon the preponderance of the one or other type of granules. There are those who firmly support Benda's view, while on the other hand there are a great many investigators who feel that an assumption of this kind, although sounding very plausible, does not rest upon a firm anatomical basis.

The posterior lobe, undoubtedly the less important of the two lobes of the pituitary gland, consists of the infundibular body, composed of neuroglial tissue without any demonstrable cells of truly nervous origin. It represents the original down-growth from the brain, and in many animals has a persistent central canal connecting with the third ventricle. In man and most higher mammals the central cavity of the posterior lobe and infundibulum becomes practically entirely obliterated. The infundibular process, extending downwards from the third ventricle, is lined by ependymal cells. The posterior nervous lobe has an epithelial investment, the 'pars intermedia' of Herring, which is composed of several layers of undifferentiated cells without blood-vessels or connective-tissue stroma. These cells elaborate the 'colloid' secretion, which is in part present in the form of vesicles or cysts and in part is to be found lying free in the meshes of the posterior lobe, whence, according to Herring's view, it finally finds its way into the ventricles of the brain. It is probably without doubt this colloid material which furnishes the physiologically active principles of the posterior lobe.

Practically all investigators who have studied the histological structure of the hypophysis have commented upon its very rich blood supply. This vascularity is particularly well seen in the anterior lobe. Dandy and Goetsch (1911) (18), from their studies of the pituitary circulation by the injection method, came to the following conclusions, which I may state in the briefest manner by quoting from their summary: 'The anterior lobe receives its blood supply from about eighteen or twenty small arteries which converge toward the stalk from the various components of the circle of Willis. These vessels immediately break



up into numerous large sinusoidal channels, in apposition with the cells and lined only by endothelium. Hence there are no veins or arteries proper in the anterior lobe. The venous supply is very similar in arrangement to the arterial system, the veins passing from the stalk to a venous circle immediately overlying the circle of Willis and draining into the *venae magnae Galeni*.

'The *pars intermedia* derives its supply from the vessels of the stalk, from the adjacent brain, and from the posterior lobe. A collateral therefore exists at this point between the anterior and posterior lobes, probably sufficient to preserve the function of at least the adjoining portion of either lobe if its individual supply is cut off.

'The posterior lobe receives its arterial supply from the small artery formed by the union of a symmetrical branch from each internal carotid. One large vein and other small ones enter the circular sinus immediately above the artery.'

A knowledge of the circulation thus helps us to understand some of the varying results obtained after different operative experiments. As an example may be cited the results of division of the pituitary stalk. Some have claimed that this is synonymous with extirpation of the gland, others that it had no effect. Realizing that there is a separate source of supply to the posterior lobe and an anastomosis with the intermediate and anterior lobe circulation, one can readily see how, in favourable instances, some or even all of the circulation of these two divisions of the gland can be carried on in spite of the interference with their supply from the stalk and by virtue of the collateral circulation from the posterior lobe. The histological structure and appearance of the hypophysis are not constant at all periods of life. There is a wide variation in the types of cells and in their relative proportions at different ages and under different physiological conditions. The chromophil cells appear soon after birth in the central portions of the gland, and of these the cyanophil or basic elements appear first, then the eosinophils. Beginning at puberty there is a marked increase in the number of chromophil cells, which continue to multiply up to the fortieth year of life, when they equal the chromophobes in number. After this period there is a gradual decrease in their number, accompanied by the formation of huge mono- or multinucleated cells with irregular nuclei and vacuolated protoplasm. By some these cells, which occur in old age, have been considered degeneration forms. In strumous individuals Schönemann found the chromophil elements increased in number even in advanced age.

It has long been known that in the later stages of pregnancy there occurs regularly a definite hypertrophy of the hypophysis with hyperplasia of its cellular elements, a condition which must be considered physiological. There is an actual increase in size and weight (Comte, 1898 (9)), especially in the anterior lobe. Erdheim and Stumme (1909) (26) showed from their studies of a long series of glands from pregnant women that the pituitary actually increased in size and weight, that there was a change of colour, particularly of the anterior lobe, from pinkish-grey to white, a fact which they attributed to an increase in chromophil elements. Histologically there is seen a marked increase of large



neutrophilic cells derived from the normal small chromophobe cells, the so-called 'Hauptzellen' or chief cells. These new cells arrange themselves in large cords or acini around the vascular spaces; they dominate the picture, while the eosinophilic cells are apparently crowded aside into the more central portions of the gland acini and are markedly decreased in number. In the later stages of pregnancy the normal histological picture is so altered that the result is most striking. Within a few months, post-partum retrogressive changes occur, the pregnancy cells return to the type of chief cells, and the gland once more assumes its normal appearance. An increase in the number of chief cells may last for several months. The hypertrophy of the pituitary in the later stages of pregnancy may become so marked that pressure may be exerted upon the adjoining optic chiasm sufficient to cause a transient bitemporal hemianopsia, cases of which have been reported from time to time. Definite changes in the face, such as temporary thickening of the nose and lips, and enlargement of the hands and feet have been reported. The glycosuria of pregnancy has been frequently commented upon. These may readily be signs and symptoms attributable to a temporary hyperfunction of the pituitary. Tardy and imperfect involutions of the gland after repeated pregnancies may lead to a kind of strumous and adenomatous degeneration similar to the colloid change in the thyroid after repeated periods of hyperthyroidism. Thus a condition which would be considered distinctly pathological is produced, followed by symptoms of 'hypopituitarism', a state dependent upon deficient pituitary secretion, to be described in a later section. It may be interesting to mention here that in certain animals, after the hibernating period, there is a definite cellular hyperplasia with mitotic figures, a fact which seems to indicate seasonal variations in functional activity of the hypophysis. Just as focal hyperplasias, which must be looked upon as pathological, may occur in the thyroid, so we find in the hypophysis focal hyperplasias of chromophil elements, both acidophilic and basophilic, and called by Erdheim (1910) (24) adenomata of the anterior lobe. According to Benda, Dean Lewis (1905) (50), later Fischer (1910) (27), these eosinophilic adenomata indicate increased functional activity, and acromegaly is the result of hyperfunction of these elements.

Certain degenerations and atrophy, followed by symptoms of deficient glandular secretion, may be dependent, as elsewhere in glandular organs, upon arterio-vascular changes; on the other hand, certain peculiar hyperplasias have been shown to follow both general and local infections.

The commonest and most important lesions of the pituitary body are the tumour growths, both solid and cystic. These may arise from the gland itself or from one of the neighbouring 'rests' of the cranio-pharyngeal duct above described. Of the tumours of the gland itself one of the common types is the so-called adenomatous struma of the chromophobe type. It may be a primary affection of the gland from the start, or it may be secondary to and a transformation from a previous chromophilic adenomatous stage, as in the late stage of acromegaly. Thus, corresponding to an early active and a late inactive stage of

the pituitary as indicated by the symptoms shown, we have corresponding changes in the histology of the gland. Along with the chromophobe strumas we always find symptoms of 'hypopituitarism', a state dependent upon an inactive gland. In this latter type of tumour the chromophil elements have entirely disappeared; there is a rapid growth and accumulation of undifferentiated chromophobe cells without definite arrangement, very little struma, and often marked vascularity. In the fresh condition the tumour is soft, pulpy, very fragile, and has a dark reddish appearance. It is these tumours undoubtedly which have often been considered 'malignant'. They do not, however, invade; metastases do not occur and mitotic figures are few. They may push upwards into the cranial chamber and cause symptoms by pressure upon important neighbouring structures, or they may cause pressure atrophy of the floor and walls of the sella turcica, fill the sphenoidal cells, and may even bulge into the naso-pharynx. At times these tumours degenerate and form haemorrhagic cysts, at other times cysts are formed with definite colloid contents, giving the appearance on section of thyroid tissue. This latter type probably arises from the pars intermedia. Teratomata, cysts, and squamous epithelial tumours have been described, all arising without doubt from embryonic 'Anlagen' of the hypophysis along the course of the cranio-pharyngeal duct. A particularly interesting tumour of this type was described by Erdheim (1909) (25), who found in a case of acromegaly a small tumour nodule, a kind of eosinophilic adenoma, situated in the middle of the body of the sphenoid bone.

#### *The Functions of the Pituitary Body.*

The functions of the pituitary body have been the subject of much speculation since the earliest times. These old ideas, many of which were purely fantastical, need not be discussed here merely to mention perhaps that the term 'pituitary' is derived from the old idea that the gland discharged a secretion—'pituita', or mucus—into the nostrils. On the part of other old writers the pituitary was regarded as the seat of the soul. In recent years the pituitary body has been considered with the organs of internal secretion, inasmuch as in foetal life even there is no definite excretory duct. The view that the hypophysis is a rudimentary gland of relatively small importance—a view held largely on account of the apparently undifferentiated nature of the posterior or nervous lobe, that part developed from the brain—has had to be given up. Recent work has shown that not only the anterior lobe, but the posterior lobe as well, possess functions of prime importance to the organism. The difficulties in determining the functions of the gland have been unusually great for a number of reasons, such as the separate anatomical divisions and the distinct histological elements in the gland, the difficulty of operative approach, the uncertainty in knowing just how much had been done in an operative way towards destroying a part or all of the gland, and the inability to obtain any active principles. As a conse-

quence the mechanism of pituitary secretion and the final decision as to its various functions remain in many respects unsettled questions.

In the earlier work are found frequent references to the similarity in structure of the hypophysis, especially the intermediate lobe and the thyroid gland, this similarity being based largely upon the presence of colloid vesicles in both. From this histological similarity it was easy to assume, as in the thyroid, that the active principle of the pituitary was represented in this secretion. Rogowitzsch (1889) (72) even suggested that the gland produced a free colloid which was at once secreted into the blood-stream. Stieda objected to this view later. Cagnetto regarded the colloid as the normal secretion of the gland and, in fact, as the last stage in the transformation of the secretion granules. He thought he saw further a certain relationship between the amount of colloid present and the number of chromophil granules in the glandular cells, namely, that with an increase in the number of secretion granules there followed an increase in the amount of colloid. Benda, on the other hand, considered the colloid as a product of degeneration and not as a final stage of secretion derived from the chromophil cells, which do not occur in the 'Markschicht' or pars intermedia, the very place where the colloid is normally found in considerable amounts. Herring (1908) (42) believes that the colloid occurring in the posterior lobe of the pituitary body is a secretion of the epithelial lining, the so-called pars intermedia, and that it passes through the meshes of the posterior lobe to the ependymal lining of the third ventricle. It then passes between the ependymal cells and escapes into the cerebro-spinal fluid, where it disintegrates with the production of a granular and amorphous debris. This author was able to show in rabbits that after thyroidectomy this colloid was increased in amount, and by careful histological methods he was able to demonstrate the path of this secretion as mentioned. Herring's histological findings have since been entirely confirmed, and furthermore, in support of his view that this colloid secretion did finally find its way into the cerebro-spinal fluid, experiments were undertaken by Cushing and Goetsch (1910) (15). They were able to show by injection intravenously into rabbits that there is a substance in the cerebro-spinal fluid which gives the same reactions as extracts of the pars nervosa itself, indicating in all probability that the active principle long recognized as being confined to this anatomical subdivision of the gland is actually secreted into the ventricular cavity. 'This would seem to establish the theory that the hyaline bodies of the pars nervosa—regarded by Herring as products of secretion of the posterior lobe, a view supported on experimental grounds by ourselves—actually discharge, as their histological appearance suggests, into the third ventricle and represent the source of the active substance resembling pituitrin in the cerebro-spinal fluid.'

Since the effects of the active principle of the suprarenal capsules have become so well known it was a natural step to extract, if possible, similar pure active substances from other glands of the body. The results of this work have not been at all encouraging. Aside from the active principle of the secretion of the thyroid, namely thyroïdin, which has no specific action on the circulatory

apparatus, no other active principles have been isolated. The depressor effect of cholin on the blood pressure should be mentioned here, and, since cholin occurs in so many secretions and organ extracts normally, it is especially confusing to one who attempts to judge of the specific glandular effects obtained by injection into animals. Many of the pressor or depressor effects on the blood pressure obtained by the injection into animals of tissue juices or organ extracts are attributable to soluble protein bodies, and hence are not at all specific.

A very pure specific principle has apparently been isolated from the posterior lobe and infundibulum by Parke Davis & Co. The fact that clinically disturbances of the genital organs are associated with pituitary disease led Frankl-Hochwart and Fröhlich (1910) (29) to test on dogs and cats the properties of this substance. They found that intravenous injections of small amounts of pituitrin in the case of the dog and cat caused contraction of the bladder musculature and increased irritability of the bladder nerves (*nervi pelvici* of the autonomic system) to faradaic stimulation. Similarly, the uterus of pregnant or lactating rabbits is caused to contract actively, and there is increased response on the part of the sympathetic nerves of the uterus to faradaic stimulation. They obtained also the well-known increase of blood pressure. Inasmuch as these effects are among the most important obtained by injection of extracts of the posterior lobe of the hypophysis, it would seem that we have here a very active principle of this anatomical division of the gland. The above-mentioned authors feel from the results of their experiments that pituitrin is practically non-toxic, and even recommend its therapeutic use in certain pathological conditions of the uterus and bladder.

By reason of the property of increasing blood pressure and causing contraction of the uterus, and possibly more on account of the latter, extracts of the posterior lobe and infundibulum have gained considerable therapeutic importance. In order to obtain a preparation of exact dosage which would possess a constant composition and therapeutic efficacy, Fühner (1913) (33) recently isolated a body which, as far as the effect on uterine contractions is concerned, represents four different constituents which have a specific action on the musculature of the uterus. These substances can be obtained in chemically pure crystals possessing uniform composition and action. This apparently active principle upon intravenous injection into rabbits causes an initial increase in blood pressure, succeeded by a longer depression, which in turn ends in a second and long-continued rise; there is a brief arrest of respiration, followed by normal respiration which later becomes intermittent. There was an increase in frequency and strength of uterine contractions, and only very slight toxicity of this active principle, which he called hypophysin. The latter was prepared chemically in the Farbwerke Meister Lucius und Brüning, Höchst a. M. Having obtained now a very pure active substance, the next step was to try it therapeutically in obstetrics for the purpose of stimulating uterine contraction. Herzberg (1913) (44), working in the Universitäts-Frauenklinik in Greifswald, found that 1 c.c. of the one per cent. solution of the sulphate of the isolated active substance of the

pituitary called 'hypophysin' corresponded to 1 c.c. of the previously elaborated pituitrin already on the market. Hypophysin was injected intramuscularly in thirty-two cases of pregnancy. The effect was seen in two or three minutes in regular powerful contractions of the uterus in all stages of parturition, and the blood loss after delivery was in no case greater than in the spontaneous births. There were no evil effects accompanying these experiments.

If we direct our attention now to the mechanism of secretion in the anterior lobe we find that there are certain very definite differences from the conditions described above in regard to the posterior lobe. Instead of the colloid, which without doubt represents the active substance of the posterior lobe, which gives such definite physiological response, and which is derived from the epithelial investment of the posterior lobe, we have here cells containing definite secretory granules and surrounded by large and numerous vascular sinusoidal spaces. There being no excretory duct of any kind, it would seem without a question that the granules are discharged into the circulating blood which surrounds the cell cords, and that the functional activity of the cells themselves depends upon the abundance of secretory granules in the protoplasm.

In attacking the problem of the functional importance of any gland there are naturally three methods of investigation available:

1. The method of direct stimulation by outside influences after the gland has been exposed by operation;
2. The extirpation in part or *in toto* of the gland substance, with consequent observations upon the animal; and
3. The method of administration of the gland substance, extracts, or active principles by mouth, intravenously, subcutaneously, or intraperitoneally.

Against each of these methods there are of course many objections that can be raised. When, however, experiments are very carefully controlled and the results of the different methods compared, very valuable and unquestionable facts are obtained.

As one of the earlier and perhaps best-known exponents of the first method, that of direct stimulation of the gland, V. Cyon (1901) (16) may be mentioned. The pituitary body, laid bare by operation, was stimulated by weak electrical currents and by the application of tampons of cotton. By this means a definite slowing and increase in force of the heart-beats could be produced, as also a slight increase in the extracranial blood pressure. He obtained much the same results by intravenous injection. Pirrone and Livon objected to these results, however, saying that they were due not to excitation of the hypophysis, but of adjacent parts of the brain or its membranes. V. Cyon states that after extirpation of the hypophysis these effects are not seen. Masay (1908) (58) repeated these experiments and obtained much the same results as V. Cyon, but was inclined to attribute them to operative shock. From his observations and results V. Cyon constructed a very elaborate hypothesis, according to which the pituitary body serves as an auto-regulatory apparatus for the intracranial pressure, and being set into activity by differences of pressure within the skull, it influences the vagus,



causing a slowing of the heart and an increase in the force of its beats, thus increasing the rapidity of flow of the blood-stream. In case of increased brain pressure by virtue of its interrelationship with the thyroid, it inhibits the supply of blood through the internal carotids, and at the same time increases the return flow through the veins. One could explain these facts much more simply and satisfactorily if one assumed that the changes in activity of the hypophysis following such stimulating influences resulted in increased secretion, which brought about the above results in a chemical way through the cardio-vascular system. In this manner many of V. Cyon's results could be brought into harmony with results of later observers to be mentioned hereafter. V. Cyon assumed also a regulating function on metabolism, believing that increased oxidation and loss of body weight were brought about by increased activity of the vagus and sympathetic systems. Finally, an antitoxic function was also assumed by V. Cyon. Later work, however, does not support such a view. In brief, then, the hypophysis was to be looked upon as a gland with a regulatory and protective function.

Schäfer (1909) (75) studied the effect upon the pituitary body of mechanical injury or of partial destruction by means of a feeble thermo-cautery. Injury of the organ, when not extensive, causes no pronounced symptoms other than increased secretion of urine, which is accompanied by increased production of colloid by the pars intermedia. This 'colloid' material contains active principles or hormones which act upon the heart, blood-vessels, and kidneys. Somewhat similar examples of the effect of injury were reported by Cushing and Goetsch (1910) (15). In several instances the pituitary gland was exposed by the subtemporal route, and a U-shaped silver clip compressed on the hypophysial stalk, which was not broken off. The result was that in the twenty-four hours following operation there was in one instance a polyuria of 320 c.c. without glycosuria, as compared with an average twenty-four hours' amount of 100 c.c. previous to operation. In another there was the surprising polyuria of 1,750 c.c. during the twenty-four hours following the operation as compared with 125 c.c., the average twenty-four hours' amount preceding operation. After the first day the polyuria rather soon disappears. It is not a question here of the operative effect *per se* nor of the anaesthetization, for in several instances in which the operation was carried out in the same way, except for the final injury to the gland, no such polyuria developed. Histologically these glands showed no especial change in the anterior lobe. The pars nervosa showed the following remarkable changes: a markedly increased cellularity, a striking hyperplasia of the epithelial investment, and hyalin 'colloid' in large amounts distributed throughout the entire pars nervosa as far up as the seat of obstruction. Above the seat of obstruction to the infundibulum hyaline bodies were present, though probably not in excessive amounts. It would seem from this that any trauma which is not entirely destructive to the posterior lobe causes the latter to become unusually active, a condition demonstrable by histological examination and apparent in the physiological expression of polyuria. An explanation of this phenomenon has seemed



to us to lie in the possible setting free and increased absorption of the colloid in the posterior lobe and infundibulum following the trauma. The facts have a very important bearing upon the clinical cases of polyuria and glycosuria frequently associated with cranial injuries, especially of the base, and with tumours in the region of the pituitary body. A discussion of their relationships will be reserved for the clinico-pathological section of this review.

The effect of another kind of injury is shown by the results of experiments carried on by Weed, Cushing, and Jacobson (1913) (85) within the past year. Having in mind the well-known effect of a Bernard *piqûre* of the hypothetical sugar centre in the fourth ventricle, they attempted to produce a glycosuria in cats by puncture in the region of the hypophysis itself, with a resultant glycosuric response (provided there was available glycogen in the system) comparable to a *piqûre* of Bernard's centre itself. They showed also that direct faradaic stimulation of the hypophysis in cats is capable of causing a marked glycosuria, prompt in appearance and enduring for some hours. The mechanism of production of glycosuria by these mechanical electrical stimulants will be considered later.

In studying the function of the pituitary body the method of extirpation in part or *in toto* has had the greatest number of adherents. Very brief mention will be made of the work of the different workers who have used this method, inasmuch as a thorough, and in fact a deserving, review of the many excellent investigations upon this phase of our problem would lead us beyond the confines of this report. In speaking of the experimental extirpation I shall draw freely from the thorough and complete report upon this subject published in 1910 (12) by Crowe, Cushing, and Homans. As stated at the beginning of their report, this method of experimentation should enable one to determine (p. 27)—

'1. Whether the hypophysis, in whole or in part, is necessary for the maintenance of life.

'2. If essential, what symptoms occur antecedent to death.

'3. If not essential to life, what effects, if any, are produced by its removal.

'4. Whether, after partial removal of the gland, definite symptoms supervene in consequence of diminished secretion, and whether a compensatory hypertrophy may occur.

'5. Finally, which of the anatomical subdivisions of the gland is chiefly responsible for the symptoms, if any, which follow the loss or mutilation of the structure as a whole.'

The results of the different investigations have, to be sure, yielded diametrically opposite results in many instances. This is to be explained by the fact that hypophysectomy represents a quite formidable operation, one where in the first place complication from haemorrhage, infection, or from injury to adjoining structures confuses the subsequent symptomatology, and where, in the second place, there is so often a question as to the totality of removal. This is due to the fact that there are intermediate lobe-cells which run up the infundibular stalk and line the floor of the third ventricle for a short distance from the

pituitary stalk, and also to the fact that embryonic rests of hypophysial tissue are frequently found in the dura of the sella turcica, in the body of the sphenoid, and in the roof of the pharynx. There is no question that these rests of tissue when left at operation may assume functional importance, and especially so when the demand for them has been created by the removal of the pituitary gland itself. The first of these factors, namely, that of haemorrhage, infection, and trauma, can be controlled, after experience, by careful modern surgical methods, and the second by serial microscopic sections of the infundibular block removed at autopsy, and containing the floor of the third ventricle, the remains of the gland and blood clot in the sella, and the dura of the floor of the sella turcica itself. The fact that these conditions have not been fulfilled has been in many instances responsible for the varying results of many of the authors.

Experimental hypophysectomy has been carried out on a variety of animals—frogs, tortoises, chickens, guinea-pigs, rabbits, cats, and dogs. The methods of surgical approach to the gland have been (1) the extracranial, (2) the intracranial. By the first method the gland was approached from below in the mid-line through the nasal, buccal, hyoid, and pharyngeal regions, or from below and to one side by a lateral pharyngeal and spheno-palatine route. Infection was the great complicating factor in this method. By the intracranial procedure the gland has been approached from above through a median opening in the cranial vault, or from the side by an opening in the temporal region with elevation of the subjacent lobe of the brain. The commonest complicating factor here seems to have been haemorrhage and trauma to adjacent parts. Crowe, Cushing, and Homans (12) (p. 230) employed a modification of Paulesco's intracranial method of approach. A generous bilateral cranial opening is made, the dura is incised on both sides, and by entering on one side and elevating and displacing the brain towards the other side the gland comes into full view in a clean field, and after some experience any desired operation can be carried out at will. In the hands of Cushing and his co-workers this method has given very satisfactory results.

Horsley (1886) (45) was apparently the first to publish a personal note regarding the experimental removal of the gland. He removed the pituitary body from two dogs, which were sacrificed at the end of five to six months respectively, and states that hypophysectomy led to no disturbing symptoms. He found that the motor cortex was exceptionally excitable in both animals.

Marienesco (1892) (57) operated upon eight cats by the buccal route. The hypophysis, so far as possible, was destroyed with a cautery. Three of these eight animals survived the operation and lived respectively three, five, and eighteen days. They lost flesh rapidly and acquired a subnormal temperature. Marienesco concluded that loss of the gland is compatible with life for some weeks.

Vassale and Sacchi (1892 and 1894) (84), by the buccal route, attempted to destroy the gland by the use of the thermo-cautery and chromic acid. All but eighteen of the twenty-three dogs and seventeen cats that were used succumbed to operative complications of haemorrhage or infection. The longest survival

was fourteen days, and it was found that the gland in this animal had not been entirely destroyed. The total removal of the gland was regarded as fatal. The symptoms observed in the fatal cases were psychic depression, apathy, motor disturbances, subnormal temperature, anorexia, loss of weight, and ultimate coma; less constant symptoms were rigidity of the hind legs, curvature of the spine, convulsions, vomiting, and polyuria. The authors concluded that the hypophysis was of great physiological importance, that its loss was incompatible with life, and that, like the thyroid, it produced a secretion in the absence of which a fatal auto-intoxication might occur.

Gatta (1896) (26), by a buccal procedure, attempted to destroy the hypophysis in four thyroidectomized cats. Death occurred in from eight to eighteen days, preceded by a failure of general nutrition and lowering of temperature, albuminuria, and rigidity of the hind legs. No microscopical control was made, but the author concluded that the hypophysis was essential to the maintenance of life.

Biedl (1897), after some similarly incomplete experiments, reached the opposite conclusion, namely, that the gland is not vitally important.

The work of V. Cyon, which appeared in a series of articles in *Pflüger's Archiv* (1898-1900), advanced his well-known views in regard to the supposed function of the hypophysis in regulating intracranial blood pressure, which have been discussed above.

Caselli (1896) (6) removed the hypophysis from a number of frogs by a pharyngeal route, without eliciting any particular subsequent disturbance, though in a few cases there occurred tetanic or epileptoid symptoms comparable to those which were found to follow intracranial operations of other kinds on these same animals. He operated likewise upon a series of rabbits by the buccal route, without success, owing to inevitable meningitis, and almost equally unsatisfactory were his later operations upon dogs and cats. In the partial removals he observed transient phenomena similar to those reported by Vassale and Sacchi. Caselli accepted Vassale's opinion that the gland was of physiological importance, it being necessary for normal development and its total loss being followed by autotoxic disturbances leading to coma not unlike that which may occur in diabetes.

Results of experiments conducted on similar lines were published in 1900 by Friedmann and Maas (1900) (31). These authors concluded from their work that the hypophysis is not essential to life, and in a later paper (1902) Friedmann emphasized this opinion and denied the retarding influence upon growth due to the loss of the gland, which Caselli had described. Lomonaco and Van Rynberk in 1901 (54) concluded from their experiments on dogs and cats that the hypophysis is not essential to life, and that the unfavourable results of hypophysial experiments were due to inevitable injury of important portions of the neighbouring cerebrum. Similar conclusions were reached by Gaglio in 1900 and 1902 (35), as a result of operations carried out upon frogs and toads by a buccal method.

Pirrone in 1903 (68) reported his attempts to remove the canine gland by the speno-palatine route, which had been so unsuccessful in Caselli's hands. He observed in six of his cases symptoms which later were recognized as symptoms of apituitarism—a characteristic depression, rigidity of the extremities with spastic gain, curvature of the spine, and fibrillary twitchings, leading to cachexia and death. He concluded among other things that a partial lesion of the gland may be compatible with life, whereas its complete removal leads to death.

Fichera (1905) reported the results of operations on forty chickens, conducted by a retro-pharyngeal route through an incision in the hyoid region, the gland being destroyed by means of the cautery. No constant or characteristic symptoms were noted, and the author concluded that in chickens the hypophysis is not essential to life, though its complete removal may retard development.

A very important contribution to the subject of experimental hypophysectomy was made in 1908 by Paulesco (65). He evolved and used an intracranial method of approaching the gland by the temporal route and divided his cases into total hypophysectomies and partial hypophysectomies. He formed the opinion that animals may live for a longer or shorter time according to the size and vitality of the remaining glandular fragment. Two of the partially hypophysectomized animals survived for five months and a year respectively without exhibiting any observable deviation from the normal. Removal of the anterior lobe alone (seven cases) he found to be equivalent to removal of the entire gland, loss of the posterior lobe (five cases) led to no appreciable disturbance whatsoever, and separation of the hypophysial stalk (six cases) from the base of the brain amounted to a complete or to a nearly complete removal as the case might be. Paulesco's experiments were very carefully controlled and added a very important contribution to our knowledge of the functions and importance of the pituitary body. He believed that the gland was essential to life.

Gemelli (1901) (37) reported his results on feline buccal operations by a method similar to the original procedure of Vassale and Sacchi. Eight of his animals survived and were sacrificed at periods varying from six months to a year. Of these seventeen were shown by most careful microscopic examination of the base of the brain and the sella turcica (decalcification) to have been subjected to a complete hypophysectomy. In one of the animals a certain amount of pars intermedia was found containing many small colloid vesicles. No especial symptoms were noted, with the exception of polyuria and polydipsia through the first few days and a subnormal temperature for the first twenty-four hours. Gemelli concludes therefore—Paulesco's observations to the contrary—that the gland is not essential to life, but that it possesses a certain compensatory function, the anterior lobe having some antitoxic properties and the posterior lobe some influence upon renal secretion.

Livon (1909) (53) performed a number of operations by the temporal route, making the serious surgical omission of not opening both sides of the skull. His primary object was to investigate the excitability of the hypophysis to various stimuli, but a few supposedly complete removals were saved for observation, the

average duration of life in these animals being thirty-six hours. The author concludes that the hypophysis is a vital organ, and that, contrary to Cyon's belief, it is not directly excitable and is not an auto-regulator of the circulation through its sensibility to pressure.

Reford and Cushing (1909) (70) reported a series of twenty operations also conducted on the lines similar to those laid down by Paulesco. The results of these observations were regarded as confirmatory of his main contention that total loss of the gland in the dog is incompatible with life. On account of the unsettled condition of the debated question—whether or not the pituitary body is essential to life—Crowe, Cushing, and Homans (12, p. 138) instituted very extensive experiments to test this point. Dogs were used almost entirely, although a separate series of feline operations was done by Homans (p. 143). The operative procedures were controlled by microscopic examination at post-mortem, and a 'total hypophysectomy' was regarded as one in which the entire posterior and anterior lobes and infundibulum were removed, leaving only a small number of cells of the pars intermedia underlying the nervous tissue still constituting the floor of the third ventricle. They concluded (p. 160), in agreement with Paulesco, that a state of apituitarism due to the total removal of the hypophysis leads inevitably to the death of the animal in about three days with a peculiar and characteristic train of symptoms (cachexia hypophysiopriva), a condition inaugurated by a premonitory subnormal temperature, followed by inactivity and unsteadiness of gait, loss of appetite, rapid emaciation, fall in blood pressure, slowing of the pulse and respiration, diarrhoea and death. A diminution in the amount of urine occurs in adults and an occasional temporary increase in the amount of urine in puppies, with glycosuria. Puppy dogs often survived total hypophysectomy as much as two and a half to three weeks.

These same symptoms after the same intervals of time follow the removal of the entire pars anterior alone, even though the posterior lobe remains in place. On the other hand, removal of the posterior lobe not only leads to none of the manifestations of cachexia hypophysiopriva, but does not appear to affect the physiological balance of the animal in any symptomatic way, unless the convulsions and excessive sexual activity which have been seen in a few cases can possibly be ascribed to its absence.

In regard to partial anterior lobe removal they conclude (p. 160): 'Definite constitutional disturbances which we may regard as manifestations of hypopituitarism have been observed after partial (anterior lobe) removal in a number of animals kept under observation for long periods of time. The most striking feature is a state of adiposity accompanied by (or resultant to?) a secondary hypoplasia of the organs of generation in adults, or by a persistence of sexual infantilism in case the primary hypophysial deficiency antedates adolescence. Polyuria, glycosuria, alterations in the skin and its appendages (such as oedemas and hypotrichosis), the tendency to a subnormal body temperature, and psychic disturbances are more or less frequent accompaniments—all of them symptoms which occasionally occur with states of adiposity and of sexual infantilism in man,



in company with certain pituitary tumours—states, therefore, which presumably are due to hypophysial (anterior lobe) deficiency.

‘Separation of the hypophysial stalk, owing to circulatory disturbances, is comparable either to a partial hypophysectomy or to a total removal with immediate reimplantation of the excised tissue elsewhere in the body. The gland becomes reattached, and the pathways for posterior lobe secretion (supposed to traverse the pars nervosa on its way to the infundibular cavity) may become obstructed by the scar, leading to an accumulation of “hyaline” within the channels of the pars nervosa’.

Paulesco regarded division of the stalk of the hypophysis as equivalent to a total, or nearly total, hypophysectomy.

In an experiment reported above (Cushing and Goetsch (15, p. 73)), in which a silver clip was compressed about the stalk, a procedure comparable to ligature, the dog remained in perfect condition and was sacrificed on the fourteenth day. Polyuria during the first few days following operation was the only symptom observable. Histological examination of the gland showed the latter to be in good condition, with no remarkable changes in the anterior lobe. The pars intermedia and pars posterior showed, however, a marked hypoplasia and increased cellularity with a tendency to increased colloid formation. Morawski (1911) (60) divided the hypophysial stalk in six apes, using the ‘overhanging brain’ method for exposure; three of the apes continued well, the three remaining died or were sacrificed some time after the operation. He regarded division of the stalk as an operation which the apes do not tolerate well, but which is not necessarily fatal. The variations which we find in the results of experimental division of the pituitary stalk may possibly be due to a large extent to the circulatory variations of the gland, to its collateral circulation, and to the amount of blood furnished by way of the floor of the sella turcica, as pointed out by Dandy and Goetsch.

Transplantation of the hypophysis and injection of its extracts were also made in animals after total hypophysectomy, with the result that the life of the animal was definitely prolonged, and in the case of the partial hypophysectomies it was possible to tide over periods of threatened cachexia hypophysiopriva in animals retaining anterior lobe fragments which temporarily may be physiologically insufficient. In the case of the total hypophysectomies a fatal outcome, however, was not prevented. Clairmont and Ehrlich (1909) (8) reported the results of their experimental iso-transplants of hypophysis into the spleen of rabbits. Histological examination of the tissue, including the point of transplant, showed that the hypophysial tissue was totally necrotic or not demonstrable at all after periods varying from a few days to several weeks. These investigations seem to have missed the well-recognized requisite that in order to have a transplant at all successful there must be a previous physiological and anatomical deficiency of the gland transplanted (Halsted, 1909) (39*a*). They concluded that the hypophysis was not adapted to transplantation.

In a report by Goetsch, Cushing, and Jacobson (1911) (38) upon experiments conducted to determine the relationship of the hypophysis, and especially of its



posterior lobe and infundibulum, to glycosuria, polyuria, and carbohydrate metabolism, they show that under various forms of operative manipulations of the infundibulum, hypophysial stalk, and often of the posterior lobe itself a transient hyperglycaemia is produced with an associated diminution in the assimilation limit for ingested carbohydrates. In many instances a transient spontaneous glycosuria was produced.

'If the operation had been so conducted as to create a subsequent and permanent insufficiency of posterior lobe secretion (either owing to the removal of a considerable portion with its epithelial investment, or through interference with its secretory discharge either by the fixation of a "clip" on the stalk or by so damaging it that an infundibular cicatrix forms) the temporary lowering of the assimilation limit is succeeded by an abnormal and enduring augmentation in the tolerance for sugars.

'The assimilation limit for carbohydrates, greatly increased under these circumstances, can be promptly lowered by the coincident intravenous or subcutaneous injection of posterior lobe extract. This extract, furthermore, has a pronounced effect in lowering the sugar tolerance of the normal animal, in whom it may even cause glycosuria when given in sufficient dosage.'

Associated symptoms observed were the tendency towards the acquirement of a generalized adiposity suggesting the conversion of the stored sugars into fat, and frequently a notable accretion in body weight. The individuals are apt to have subnormal body temperature, suggesting an imperfect oxidizing or metabolizing capacity, and this persistently lowered temperature can be raised by the injection of glandular extracts. These observations proved at once to have a very important clinical bearing, a point which will be discussed further in the subsequent sections of this review. Aschner (1912)(1) gave a very full report of the results of his studies on the varied effects of hypophysectomy on dogs. He used the buccal route to expose the gland. His conclusions in brief were as follows :

In adult dogs the trophic changes are very slight, often hardly perceptible. Aschner believes that total extirpation of the hypophysis is compatible with life if the base of the infundibulum be uninjured. The younger the animal at the time of the hypophysectomy the more outspoken are the trophic changes. In adult dogs the only changes produced are: some general depression, slightly subnormal temperature, slight diminution in adrenalin glycosuria, a lessened general resistance, slight damage to the sex-glands, and a diminished sexual activity. Aschner attributes some of the effects observed in previous investigations to cerebral trauma, especially in the region of the tuber cinereum.

In young animals hypophysectomy leads to very marked and characteristic changes. There is a marked retardation in growth, diminished general activity, a certain psychic depression, subnormal temperature, the hair remains more of the puppy type, the skin is thicker and less elastic, persistence of the milk teeth, failure of the epiphysial lines to close, a more delicate and undeveloped condition of the skeleton. The blood-vessels are very delicate. There is an

apparent increase in size of the alveoli in the thyroid with excess of colloid, an abnormally persistent thymus, fatty infiltration into the liver, increase in thickness of the adrenal cortex, failure of development of the sex apparatus and sexual activity in both males and females. Hypophysectomy during pregnancy causes abortion. Aschner regards the anterior lobe as mainly responsible for these changes.

In regard to metabolic disturbances he found that there was marked diminution in the nitrogen excretion in hypophysectomized dogs. The amount of adrenalin necessary to produce glycosuria was greater, but no especial change in the glycosuria obtainable with phloridzin was noticed. There was diminished oxygen consumption per kilo of body weight as compared with the normal. Benedict and Homans (1912) (3), in a very thorough and comprehensive study of the metabolism of hypophysectomized dogs, found that there was a marked fall after operation of the total metabolism as measured by the carbon-dioxide production, and that the fall in carbon-dioxide production per kilogram of body weight per hour is still more noticeable owing to the deposition of inert body fat.

The third and final method of investigation consists in the administration of fresh gland, dried extracts, fluid extracts, or active principle in one way or another. The hypophysis of various animals was used for this purpose, such as the ox, horse, cat, dog, sheep, and even man. At first extracts were made from the whole gland, and later from the anterior and posterior lobes separately. These extracts were given by mouth, intravenously, subcutaneously, or intraperitoneally. The results of these investigations were often contradictory, and final statements in regard to some of the properties of pituitary extracts must still remain open.

In 1895 Oliver and Schäfer (63) reported the results of their researches, which demonstrated in the mammalian pituitary body an active principle which has a specific effect upon the heart and blood-vessels when injected intravenously. It was shown that it produced a general constriction of arterioles, leading to considerable elevation of blood pressure and an augmentation of the force of the heart-beats. No distinction was made between the lobes of the gland.

Howell (48, p. 248) pointed out that it is the posterior lobe alone which possesses this property (1898). In general the course of the curve when the vagi were intact was as follows: 'Within a few seconds (5-10) after the beginning of the injection the blood pressure rose to a variable extent; this was followed quickly by a temporary fall, which was also quite variable; in some cases it lasted for a few seconds only, while in one instance it continued for nearly a minute. This phase was then succeeded by the main effect, namely, a very marked slowing of the pulse-rate that lasted for a long time, in some cases over half an hour. The maximum slowing was attained gradually and the return to the normal rate was made still more slowly. During this period the maximum blood pressure first increased slowly, rising usually to a level above that pre-

vailing at the time of the injection, and then slowly dropped back to normal.' Subsequent injections soon repeated had little or no effect.

Magnus and Schäfer (1906) (56), and later Schäfer and Herring (1906) (76), showed that extracts of the posterior lobe have the additional characteristic of producing kidney dilatation and diuresis when injected intravenously. There seemed also to be a substance in the extract which acts by directly stimulating the secretory activity of the cells.

Herring (1908) (43), in a comparative study of mammals, birds, and bony fishes, found that the extracts of the anterior lobe had no immediate physiological action when injected into the blood-vessels. Extracts of the posterior lobe of birds and bony fishes gave an action similar to extracts of the mammalian posterior lobe, bringing about a rise of blood pressure, expansion of the kidney, and an increase in the secretion of urine. Extracts of the pituitary body of elasmobranchs have no immediate physiological activity. He suggested also that the posterior lobe poured its products into the infundibulum, and so into the ventricles of the brain.

Salvioli and Carraro (1908) (73) confirmed the most important findings of previous authors, and concluded that the posterior lobe is the physiologically active part of the gland, that its extract at first has a slight depressor followed by a longer pressor effect upon the blood pressure, that it causes increased strength of the ventricular beats and slowing of the pulse, that the effect of repeated injection becomes markedly less. The respiration is not modified appreciably; the extracts are not very toxic; the hypertension is produced by constriction of the vessel walls, not by exciting vaso-motor centres; the slowing of the pulse is due to direct action on the vagus centre; inasmuch as this action is still present when the vagi are cut one must suppose that there is also a direct action on the ganglia or on the muscular fibres of the heart.

Contrary to the findings of all previous authors Hamburger (1910) (40) described a depressor effect on the blood pressure and an acceleration and weakening of the heart following intravenous injection of a saline extract of the hypophysial anterior lobe. With alcoholic extracts a secondary rise above the normal followed the depressor effect.

Lewis, Miller, and Matthews (1911) (51) undertook to determine the origin of the pressor substance in the hypophysis and its mode of secretion, and of reconciling, if possible, the divergent views concerning the depressor substance in the anterior lobe. They found that extracts of the *pars intermedia*, the epithelial investment of the posterior lobe, when injected intravenously, caused a decided rise in blood pressure. They confirmed Howell's previous findings in regard to extracts of the posterior lobe. Extracts of the anterior lobe they found to give a primary fall, which was followed in the majority of instances by a secondary rise in pressure above the level existing at the beginning of the experiment, thus confirming Hamburger's previous findings. They believe, as many previous authors, that the pressor substance is secreted by the *pars intermedia* and that it then passes into the *pars nervosa*.

An interesting finding was pointed out by Crowe, Cushing, and Homans, namely, that anterior lobe extract elicited a characteristic febrile response when injected subcutaneously in animals with experimental pituitary deficiency.

Ott and Scott in 1910 (64) found that infundibulin, or the active principle of the posterior part of the hypophysis, when injected into the ear vein of the goat in the early nursing period increased the secretion of milk. Mackenzie in 1911 (55), in studying the mechanism of milk secretion, showed similarly that extracts of the posterior lobe acted as a mammary stimulant and that anterior lobe extracts were inactive in this respect.

A question of considerable experimental and clinical interest and importance is that of the relationship of the hypophysis to the production of glycosuria. Borchardt (1908) (4), in working on rabbits, showed that it was possible to produce a glycosuria by the injection of extract of horse hypophysis. It was considerably more difficult to produce glycosuria in dogs. A hyperglycaemia was noticed in some instances. He suggested a possible relationship between glycosuria and hypophysis in cases of acromegaly.

Franchini (1910) only occasionally produced glycosuria in rabbits by gland injection. In applying Ehrmann's test for adrenalin to the freshly excised frog's eye, Borchardt (1908) (4) found that pituitary extract similarly had a mydriatic effect. The question of whether this action is due to stimulation of the sympathetic or oculomotor fibres is apparently still an unsettled point.

Cramer (1908) (10) showed definitely that it was the extract of the posterior lobe which produced the mydriatic effect upon the pupil of the enucleated frog's eye, and Franchini (1910) showed that the anterior lobe extract was inactive in this respect, pars intermedia had a slight mydriatic effect, and posterior lobe a well-marked one. All the separate extracts gave negative adrenalin tests with ferric chloride (Vulpian) (green) and with sublimate solution (Comesatti) (red), indicating also that the active principle of the posterior lobe resembles adrenalin in some of its properties, but does not give all of its reactions.

Repeated subcutaneous injections of sterile extracts, or emulsions of the whole gland or of the posterior lobe alone given subcutaneously, are apt to lead to emaciation (Crowe, Cushing, and Homans, 1910) (12), indicating a stimulus to katabolic processes, a condition, as we have seen, opposite to that described after partial extirpation of the pituitary. They also showed, as did Carraro (1908) (5) previously, the tendency to severe hepatic necroses after repeated injections of posterior lobe extract. Large doses or oft-repeated doses are undoubtedly toxic.

Caselli (1900) noted no effect on growth after long-continued injections of whole gland glycerin extracts. A noted retardation of skeletal growth with epiphysial changes has been noted by some other authors. The thyroid has been described as undergoing a cellular desquamation and hyperplasia after these repeated injections.

Franchini (1910) found that extracts of ox and horse hypophyses, and of the posterior lobe in particular, produced very notable alterations in the mineral

metabolism, and led to a marked deficit of calcium, magnesium, and in less degree of phosphorus. In the circulating blood it causes increase of calcium and magnesium. Besides its toxic action on rabbits and guinea-pigs in general, it causes also ulcerations of the intestinal tract with haemorrhages.

Attempts have been made to simulate conditions of hyperpituitarism by feeding with fresh gland or glandular extract over long periods of time. This feeding must naturally be done in young animals and controlled carefully by taking animals of the same litter. Different results have been obtained by different investigators. Caselli (1900) (6) states that it retards growth. Sandri's experiments (1909) on feeding young rats with bovine anterior lobe were quite negative, whereas posterior lobe feeding arrested development—an effect attributed to the toxicity of the active principle. In Schäfer's (1909) (74) experiments with the feeding of the pituitary substance (anterior lobe) to young rats there seemed to be a definite increased growth of those receiving the gland extract as compared with the controls. There was definitely no retardation of growth. In some unpublished experiments we have been able to confirm Schäfer's results.

Within very recent times the relationship between the hypophysis and the nervous system has received considerable attention. Mention has been made above of the probability that pituitary extract (posterior lobe) exerts its influence particularly upon the heart and circulatory mechanism, through its action upon the vagus and its centres. Later it was shown (Howell) that the same effect was produced after section of the vagi, but to a less extent, indicating a possibility of direct action of the extract upon the heart and blood-vessels. It would seem that both modes of action might be possible. Within the past year Weed, Cushing, and Jacobson (1913) (85) conducted a series of experiments for the purpose of studying the relation of pituitary activity to sympathetic nervous control. They showed (p. 50) that 'The pituitary body, and more particularly its posterior lobe, plays a significant rôle in the metabolism of carbohydrates, and its action in this respect is under the control of fibres which reach the gland by way of the superior cervical sympathetic ganglion. Stimulation of this nervous pathway at the so-called sugar centre in the fourth ventricle at the superior cervical ganglion, and by excitation of the pituitary body itself, liberates a chemical substance which causes glycogenolysis and glycosuria, independent of any possible nervous impulse reaching the glycogen-holding cells of the muscles or abdominal viscera.'

It has been shown by a great many different authors that partial or total removal of the thyroid, parathyroids, testes, pancreas, or adrenals, is followed by histological changes in the hypophysis, usually of a hypertrophic or hyperplastic nature and accompanied often by symptomatic evidences of pituitary hyperfunction. Similarly, after extirpation of the hypophysis, secondary changes occur in many of these ductless glands, accompanied by symptoms referable to a disturbance of one of the ductless gland series rather than to the primary hypophysial deficiency (Cushing, 1912 (13), p. 275). These facts have led to the well-known prevalent view at the present time that a close interrelationship



exists between members of the ductless gland series, and that disturbances in the function of one are followed not only by symptoms referable to this one gland primarily involved, but also to one or more of the other ductless glands secondarily involved.

Interrelation between hypophysis and testis or ovary appears on clinical as well as experimental grounds to be more intimate than that between any other two members of the series. We have found that after a partial hypophysectomy (anterior lobe) in the puppy there is a very marked and permanent diminution in the number of Leydig cells and a retardation or complete cessation of development of the spermatogenous epithelium. In pre-adolescent castration reproduction is of course impossible and the acquired characters of sex fail to appear. Tandler (1910) (82) has pointed out that the special growth features of eunuchism under these circumstances may be a consequence of the hypophysial hyperplasia which is known to follow castration. Clinical examples of this interrelationship will be given later. What has been said here in regard to the testis applies equally well to the ovary, where we have two glandular elements, the follicular epithelium and the interstitial cells, comparable to the spermatogenous epithelium and the interstitial cells of Leydig. It is very probable that these two elements in the cases of both testis and ovary may be affected independently, giving rise to very different end results.

*The thyroid* (Cushing, p. 260) (13 a). It is our impression that a transient active hyperplasia occurs as a result of a total or nearly total extirpation, and that this condition is ultimately succeeded—if the animal survives for any length of time—by a functional involution, in which an excess of colloid and low epithelium is shown under the microscope. The hyperplasia suggests that the two glands are capable of a synergic action; in other words, that 'either can, to some extent, in case of need, function vicariously for the other' (Hoskins, 1911) (46). Rogowitsch (1889) (71) found that the pituitary body hypertrophied after thyroidectomy in the rabbit, and suggested in explanation that this organ was functioning vicariously for the thyroid. Mention has been made of the findings of Herring (1908) (42), who confirmed the results of Rogowitsch and showed further that there followed a definite increase in the amount of colloid in the posterior lobe and a hyperplasia of the pars intermedia. Degener (1913) (19) showed that after complete thyroidectomy in adult rabbits there was a definite increase in size and in weight (proportionate to body weight) of the pituitary, the more remarkable the longer the interval intervening between thyroidectomy and the death of the animal.

No definite evidence, histological or symptomatic, has thus far been offered to show that the parathyroid glandules participate in the general disorders, experimental or clinical, of the pituitary body. The relationship of both glands to mineral metabolism, especially that of calcium, need only be mentioned.

The observations pertaining to a relationship between pituitary and adrenals are fewer. Certain similarities in the action of their products, as mentioned above, seem to indicate this. 'Hallion and Alquier have noted hyperplasia of



the adrenal cortex after prolonged feeding of pituitary extract. After intraperitoneal injection of a similar extract, R  non and Delille have obtained the same result. In both cases the posterior lobe alone was effective' (Hoskins, p. 44) (46). From the clinical side many cases of hypophysial insufficiency have been observed and reported (Cushing, p. 281) (13) which showed symptoms very suggestive of functional insufficiency of the suprarenal bodies, pigmentation of the skin, asthenia, low blood pressure, and to these may be added hypoglycaemia.

In regard to the thymus, Cushing (p. 282) (13) says, 'Our clinical experience would lead us to believe that in cases of primary hypophysial insufficiency there is apt to be a persistent and enlarged thymus when the process dates from the pre-adolescent era, and possibly that there is some hyperplasia of the involuted gland in cases which appear to have originated in adult life. This corresponds, roughly, with our experimental findings in the dog, for a seeming enlargement of the thymus, especially rich in Hassall's corpuscles, has been found in most of the animals, puppies as well as adults, who have long survived an extensive deprivation of the hypophysis.'

No certain histological changes have been observed in the pancreas as a result of disturbances in pituitary function. We have found that removal of the pancreas in dogs causes an increase in 'colloid' in the pars intermedia and in the posterior lobe, that injection of posterior lobe extract will cause a diminution in carbohydrate tolerance, and that removal of the posterior lobe causes a marked increase in carbohydrate tolerance. The diabetes of pancreatectomy is well known. All these facts point to some interrelationship between the two glands, antagonistic perhaps, nevertheless quite definite.

A definite interrelation with the pineal gland has not been demonstrated.

Attempts have been made to construct a scheme or system of interrelationship of the various ductless glands one with another and with the vegetative or sympathetic nervous system. The stimulus for this has come largely from the Vienna School, in the first instance from the work of Eppinger, Falta, and Rudinger (1908-9) (21), and later from Biedl and several others. Aschner (1912, p. 108) (1) added the hypophysis and the ovary to the original scheme and placed the former in a position analogous to that of the thyroid. He states that the pituitary hypofunction inhibits, while hyperfunction stimulates the chromaffin system, as in the case of the thyroid. Evidence for this lies in the fact that after pituitary extirpation adrenalin glycosuria and other signs of sympathetic stimulation are obtained with considerably greater difficulty. On the other hand, it may be stated here that in acromegaly in its early stages, where pituitary hyperfunction is assumed, glycosuria is frequently found. This may be due to splanchnic stimulation of the adrenals. There seems to be a certain antagonism between pancreas and hypophysis, for after extirpation of the latter pancreatic diabetes is inhibited. In this connexion we have found that dogs with extirpation of the posterior lobe of the pituitary tolerate removal of the pancreas better than normal animals.

*Clinical and Clinico-Pathological Considerations.*

In this third and last division of this review I could do no better than to follow the general outline of this phase of the pituitary problem as given in Cushing's (1912) (13) comprehensive monograph on the subject of 'The Pituitary Body and its Disorders', and in presenting this side of the subject I shall borrow freely from it.

*Symptomatology.* In considering this interesting subject, Cushing, p. 237, divides the symptoms manifested by the numerous patients who have come under his care into—

1. Neighbourhood symptoms ;
2. General pressure manifestations ;
3. The secretory or glandular symptoms proper ; and
4. The polyglandular manifestations.

Before taking up these divisions in greater detail it may be well to define certain terms which have come into common usage. It has been found convenient to apply to the clinical types of pituitary disease certain terms which express at the same time our conception of the activity of the gland in these states of disordered function. In the case of the thyroid a definite symptomatology was established for conditions of overaction of the gland and called 'hyperthyroidism', with exophthalmic goitre as the well-known example ; similarly for conditions of under-activity of the gland, called 'hypothyroidism', and exemplified by myxoedema in the adult and cretinism in childhood. Just so analogous terms were chosen for states of over-activity of the hypophysis—'hyperpituitarism'. Practical difficulties were, however, encountered in attempting to place all types of pituitary trouble in these two groups, for conditions of presumed primary over-activity frequently go over into states of under-activity, so that symptoms characteristic of both states blend one with another, just as in the case of the thyroid we have symptoms of myxoedema engrafted on the picture of Graves's disease. Then again, in the pituitary we are dealing with two separate lobes, either one of which may become the seat of disease without the involvement of the other, or one may become adenomatous and clinically overactive, and by pressure upon the other lobe may impair its function and cause a condition of under-activity of this part. To designate this large group of pituitary diseases the term 'dyspituitarism' has been used.

In coming back now to the symptomatology proper, we find neighbourhood symptoms spoken of as those dependent upon pressure upon parts in the immediate neighbourhood of the pituitary. These are occasioned mostly by hyperplasias or tumour growth of the gland itself. They are headaches, usually bitemporal and presumably due to distension of the dural envelope of the gland. Photophobia is occasionally complained of.

In pituitary enlargement one of the first structures to suffer is the sella turcica, from distension and pressure atrophy. In the diagnosis of the bony changes in the region of the sella the examination by means of the X-ray has

become indispensable. A valuable contribution to this subject has been made recently by Schüller (1912) (79). Cushing (13, p. 238) has distinguished three types of the pathologically deformed and enlarged sellas:

- (1) those associated with thickening of the clinoid processes and dorsum;
- (2) those with thinning from pressure absorption of these parts; and
- (3) those with more or less destruction of all outlines.

These are the types of sellar change dependent largely upon growths primarily intrasellar. Great difficulty in diagnosis is, however, met with in those cases of tumour in the interpeduncular region arising from the pituitary stalk and situated above the sella—the so-called superimposed tumours. The latter lead to sellar changes only after they have reached considerable size. Unusual difficulties of interpretation are also met with in those cases of abnormally small sellas occurring in conditions of primary glandular hypoplasias.

The most common and the most serious of all neighbourhood signs are those following pressure upon the optic nerves, either from an extension of an intrasellar tumour beyond the confines of the sella turcica or from a primary infundibular growth. Primary optic atrophy follows, the disk showing no oedema except in the late stages, when the growth has reached such a size as to cause a general increased intracranial pressure. In this manner a choked disk may be superimposed on a primary optic atrophy. Distortions of the visual fields are also frequently seen. The supposedly typical bitemporal hemianopsia is not as common, however, as one might at first believe. Homonymous defects and unilateral blindness without involvement of the opposite eye are fairly frequently found. Tendencies toward temporal defects, and especially in the colour fields, are of great importance in making an early diagnosis, for these may be present long before one can demonstrate a complete hemianopsia. Pupillary changes are found, associated of course with the optic atrophies and perimetric changes. The oculomotor nerve may be implicated in the extension of an intrasellar growth or from a primary interpeduncular one, and may thus lead to periods of temporary diplopia in the early stages and to strabismus later. An interpeduncular growth or a large extrasellar one may furthermore cause trigeminal neuralgia by pressure upon the fifth nerve, uncinate seizures with gustatory or olfactory aura following pressure upon the uncinate region, and symptoms referable to direct implication of the frontal lobes. In many instances naso-pharyngeal signs are also found, such as epistaxis, intermittent discharge of mucus into the naso-pharynx arising from the sphenoidal cells, and a cerebro-spinal rhinorrhoea.

*General pressure symptoms.* These follow upon a general increase of intracranial tension. Headache is a common symptom, whereas vomiting is far less common. There is frequently a choked disk superimposed upon a primary optic atrophy, but this need not necessarily be the case, for an intracranial extension of a sellar tumour may so firmly envelop the optic nerves as to prevent the escape of cerebro-spinal fluid from the cranial chamber into Schwalbe's sheath, thus preventing the formation of a choked disk. There may

be distension of the veins of the scalp and of the eyelids. The X-ray has again been of value here in showing signs of pressure enlargement of the diploetic channels, points of pressure atrophy due to small arachnoidal herniations, and convolutional pressure markings on the inner surfaces of the bones of the cranial vault.

*Glandular manifestations.* A study of the rôle of the hypophysis in growth is a very interesting one. The results obtained by the various investigators are far from uniform. From the experimental side facts have been brought forward which are of a negative nature, however; i. e. it has been shown that hypophysial deficiency inhibits skeletal development. States of functional over-activity are more difficult to obtain and can possibly in part be stimulated by the feeding with glandular extracts. Increased growth has apparently been obtained by some by feeding pituitary extract to young animals. The view that acromegaly and gigantism are attributable to a functional hyperplasia of the pars anterior, although receiving firm support from many, is not universally accepted. The more important theories regarding the causation of acromegaly have been:

1. The 'hypopituitarism' theory. According to this view acromegaly is due to diminished hypophysial function. This was the view championed by Marie (1888-9).

2. The 'hyperpituitarism' view, held by Tamburini (1894) (81), Benda (1901) (2), Fischer (1910) (27), and others, who pointed out that the condition is often associated with a hypertrophy or adenomatous hyperplasia of the gland, whereas destructive lesions do not produce it. According to Benda, Lewis (1905) (50), and Erdheim, there is an actual hyperplasia of the chromophil cells, the relative proportion of the latter to the chromophobe cells is increased, and there need be no gross increase in size of the gland.

3. According to this view acromegaly is due to some underlying nutritional disorder which affects the general metabolism; the hypophysial tumour or hyperplasia may be the fundamental sign or symptom, but in association with the remaining abnormal findings. This view has been supported by Strümpell, Vassale, and Cagnetto.

4. There are those who point out cases of acromegaly in which there have been presumably negative findings in the hypophysis and conclude that the relationship between the two is only an occasional and accidental one.

The various arguments which have been brought forward to support one or the other view will not be considered at this point. It may be stated, however, that the view which regards acromegaly as due to hyperpituitarism seems in the light of present-day knowledge to be the most likely one. If the condition of hyperpituitarism occurs fairly early in life, before the closure of the epiphysal lines, a condition of general skeletal overgrowth occurs, resulting in the condition known as gigantism.

*Skeletal undergrowth.* If glandular insufficiency occurs before full stature is attained, that is, especially before adolescence, skeletal undergrowth results,

similar to deficiency states of other members of the ductless gland series, as the thyroid, adrenal, and thymus. In this condition there is not only failure of development of the long bones, but there occurs also a feminine type of body configuration with a broad pelvis and a tendency to genu valgum.

*Cutaneous and subcutaneous changes.* In hyperpituitarism these are of a hypertrophic type. There is an increase in thickness and density of the skin, a connective-tissue increase in the subcutis, an enlargement of the hair follicles and of the secretory glands of the skin. Hypertrichosis is frequently seen.

In primary hypopituitarism the skin is smooth, transparent, and free from moisture, the axillary and pubic hair is very scant or almost entirely absent, the nails are small and thin. Pigmentation may occur; an excessive subcutaneous deposition of fat is a notable feature of some of these cases and may lead to a marked degree of adiposity. This latter sign has been ascribed to posterior lobe deficiency.

*Hypopituitarism in childhood.* In recent years, besides acromegaly, another important group of cases which present a very similar clinical syndrome have become associated with functional changes in the hypophysis. The cases are those which show a rather general adiposity coupled with genital dystrophy and skeletal under-development. The disposition of fat in these cases is especially to be seen about the loins, thighs, pubes, abdomen, and pectoral regions. They have been called cerebral adiposities, for in many cases they have followed tumours of the hypophysis. There are several types, which differ in the character of dysgenitalism which they show and in the presence or absence of overgrowth. In the type of Fröhlich (1901) (32) there is a stunting of growth together with a hypoplasia of the genitals, a condition to which the term 'dystrophia adiposogenitalis' has been applied. The presence of a hypophysial tumour has been demonstrated in many of these cases. It has become evident, however, that a tumour of the hypophysis is not the only condition which may be responsible for these clinical syndromes, inasmuch as a primary hypoplasia, especially of the posterior lobe, or even an internal hydrocephalus, capable of producing a hypophysial deficiency, may be responsible for the clinical syndrome of adiposity and genital hypoplasia.

*Adolescent types.* When the condition dates from puberty it is associated in the male with juvenile skeletal configuration or with feminine outlines. There is a corresponding disposition of fat and scantiness of body hair. In females there is a coincidental amenorrhoea.

In adults the adiposity is still present, though perhaps not so striking, and genital hypoplasia is common.

Recent studies in hypophysial adiposities have stimulated a renewed interest in Dercum's disease, or the so-called adiposis dolorosa. By many the latter has been regarded as closely related to the above types of adiposity, and by some to be actually due to hypophysial deficiency. In one of Dercum's cases at autopsy McCarthy (1902) (20) found an adeno-carcinoma of the pituitary body, with testicular hypoplasia.



The relation of pituitary function to carbohydrate metabolism has been considered above under the section on experimental hypophysectomy. Clinically it has been found that in the early active stage of acromegaly there is often a spontaneous glycosuria, and that in the later stages, when symptoms of hypopituitarism intervene, such as subnormal temperature, dry skin, adiposity, low blood pressure, there is to be found a high carbohydrate tolerance, as much as 400 grm. of glucose or levulose being ingested without consequent glycosuria. In the cases of primary hypopituitarism a high sugar tolerance is present from the beginning.

*Polyuria and polydipsia.* The facts which have been learned experimentally in regard to the relationship between pituitary and renal secretion have cleared up in many respects the obscure polyurias of encephalic origin. In an earlier section of this review a report of the work of Schäfer and Magnus was given, which showed that extracts of posterior lobe possessed diuretic properties. It was stated also that posterior lobe removal, or in fact any injury to the infundibulum, produced a polyuria of some days' duration in dogs. Subcutaneous implantation of the gland can also cause a polyuria. Clinically it has long been known that intracranial tumours and cerebral syphilis accompany diabetes insipidus, and, according to Fletcher (1902) (34), primary optic atrophies and hemianopsias have frequently been observed in these cases. At various times authors have commented upon the occurrence of polyuria in association with interpeduncular tumours. In a recent report, Cushing (1913) (14) has taken up fully the relationship of diabetes insipidus with pituitary disease and cites a number of instances of remarkable polyuria in association with hypopituitarism cases, especially with tumour, and mentions also cases of marked increased urinary output following simple sellar decompression of the gland. All these facts make it evident that many of the present-day conceptions in regard to diabetes insipidus will need revision in the light of recent investigations on the functions of the pituitary body.

*Variations in body temperature.* Many of the cases of hypopituitarism have shown a slightly subnormal temperature, and in a few instances of severe grades of glandular insufficiency the fall in body temperature has been very marked. These patients often complain of suffering from the cold, the pulse is correspondingly slowed, and the whole picture suggests that of diminished metabolic activity. The lowered temperature can be raised by administration of anterior lobe extract by mouth, and upon subcutaneous injection of the extract in these cases a febrile response of two or three degrees can be produced. This thermic response may be of some diagnostic value in the diagnosis of hypopituitarism. No such reaction follows the ingestion or the subcutaneous administration of posterior lobe extract.

A low arterial tension is a common finding in states of pituitary insufficiency. The systolic pressure registers often in the neighbourhood of 90-100 mm. Hg., and in the later stages of asthenia may fall as low as 70 mm.

In many, in fact in almost all of the cases of hypopituitarism, patients show a tendency to drowsiness and torpidity.



There is an inclination to doze throughout the twenty-four hours; in some instances periods of somnolence occur in definite cycles, with intervening days in which the sensorium is clear and bright. In these cases associated with a primary pituitary lesion administration of gland extract has markedly improved the general condition and definitely lessened the drowsiness. The reverse picture, which one might expect in hyperpituitarism cases, has not been definitely recognized. General insensitivity and constipation have been other troublesome symptoms.

Evidences of psychic irregularities are also to be seen in many cases of pituitary disease. These may be due to (1) pressure upon the temporal or frontal lobes by a growth arising from or in the neighbourhood of the gland, or to (2) the effect of excessive or diminished secretory activity of the pituitary gland. The frontal lobe may be encroached upon with a resultant change in disposition, enfeeblement of memory, disorientation, and untidiness. An early symptom is often a complete indifference to the existing condition. Pressure upon the temporal lobe may cause attacks referable to irritation of the uncinate gyrus and ushered in with olfactory and gustatory aura, and leading into the so-called 'dreamy states' frequently seen.

In conditions of hyperpituitarism certain temperamental changes, such as wakefulness, lack of concentration, indecisiveness, irritability, distrust, and others, are apparent.

In hypopituitarism there are to be found all stages from mild psychoses to profound mental disturbances with epilepsy. In these conditions glandular feeding has often given benefit. The suggestion has been made that as a result of hypophysial insufficiency there may possibly be a predisposition to cortical instability.

In the consideration of experimental hypophysectomy mention was made of the fact that primary hypophysial deficiency produced certain changes in various of the other ductless glands, and that the resultant symptoms might in part be due to secondary changes produced in these glands. Similarly, the reverse also held true, that is, removal of other members of the ductless glands produced certain definite changes in the pituitary body. Clinical examples of this interrelationship are now frequently recognized. The interrelation between hypophysis and testis and ovary seems to be especially close, and probably more intimate than between any other two members of the series. There are numerous examples of imperfectly acquired secondary sexual characteristics when the hypophysial lesion antedates puberty, and of amenorrhoea or impotence with genital hypoplasia when the pituitary deficiency develops after the acquirement of adolescence. Castration, on the other hand, has been shown to produce hypertrophy and hyperplasia of the pituitary, and to be followed by the special growth features described by Tandler as characteristic of the eunuchoid type. In the early and therefore supposedly active stage of acromegaly an excessive sexual libido has not been an uncommon symptom.

Certain retrogressive changes have been described in the hypophysis in cases

of exophthalmic goitre, and in colloid goitre cases Schönemann has described a senile eosinophilic condition of the hypophysis. Many of the cases of pituitary disease have been found to have a small thyroid, with low epithelium and excess of colloid. Definite changes in the parathyroids have not been found.

Certain symptoms of dyspituitarism, such as pigmentation of the skin, asthenia, low blood pressure, and hypoglycaemia, suggest the participation of the adrenals in the polyglandular syndrome. In some of the cases the adrenals have been found to be exceedingly small, and on histological examination there has been found a marked vacuolization of the cells of the zona fasciculata of the cortex, suggesting some peculiar lipoidal change, or perhaps an excessive accumulation of a normal secretion of the cells.

In states of primary hypophysial deficiency antedating adolescence the thymus has been frequently found to be abnormally large and persistent, and a lymphatic hyperplasia has been described. These are, however, not by any means constant findings. Histological changes in the pancreas and pineal have been less definite.

#### *Treatment.*

The therapeutic problem presented may call for (1) mere symptomatic medicinal measures, (2) operative relief, and (3) for the administration of the glandular extracts to make up for a deficient secretion. In one case sellar decompression of a pituitary tumour may be necessary to relieve the headaches due to distension of the dural envelope of the gland, another may require partial extirpation of a struma to relieve pressure on the optic pathway, and another free from neighbourhood pressure symptoms may require simply glandular feeding.

Variable surgical procedures must be used to meet the variable operative conditions met with. They comprise those (1) directed towards the relief of general pressure symptoms, (2) those intended to lessen the excessive secretion by partial extirpation, and (3) those directed toward the relief of neighbourhood pressure symptoms.

A subtemporal decompression is indicated in those cases where the general pressure disturbances are so severe as to demand palliative treatment before the primary tumour itself can be attacked.

Partial extirpation of the hyperplastic gland has been suggested in the early stage of acromegaly, to combat the excessive glandular activity, a procedure previously carried out in the case of the thyroid gland for the treatment of hyperthyroidism. Schlosser (1906) (77) was the first to suggest partial extirpation of the hyperplastic pituitary as a means to check the progress of acromegaly. The procedure has been carried out in a number of instances with marked improvement. Inasmuch as the hyperplastic gland tends to undergo involution and become hypoplastic spontaneously, operative measures are not so promising in the absence of associated neighbourhood pressure symptoms. For a full discussion of the evolution of the methods of surgical approach to the gland I should

like to refer to Cushing (1912) (13), p. 292. At this point I may say that, in the modern operations used and approved by Cushing, a sublabial approach is made, a submucous resection is done of the lower nasal septum, at the same time pressing the turbinates to the sides but not removing them, the sphenoidal cells are opened and removed, the floor of the sella turcica taken away, the dural envelope of the gland incised, and a partial removal of the struma done. This allows for decompression and encourages downward growth and displacement of the growth with a more complete removal through the nose at a secondary operation, if this becomes necessary. The normal restoration of the nose and lip is complete, there being no post-operative discomforts whatever.

Glandular implantation for the benefit of severe grades of hypopituitarism have not thus far been attended by any great success.

The administration of glandular extracts has been attended in many instances by marked improvement. Treatment with the X-rays, in the case of struma of the rapidly enlarging type especially, has been attended in many cases by the relief of tension symptoms, due in all likelihood to a shrinkage of the growth. It is frequently advantageous to supplement operative treatment by the use of the X-ray.

In conclusion, I desire to express my thanks to Prof. Harvey Cushing for the free use of his large collection of reprints upon various phases of pituitary work.

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It is desired to call attention to the excellent review by Dr. Arthur Münzer, 'Die Hypophysis,' *Berl. klin. Wochenschr.*, 1910, xlvii. 341, 392, which was helpful in many ways in preparing the above review.



## OBSERVATIONS ON PAROXYSMAL TACHYCARDIA

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With Plates 19-24

THE term paroxysmal tachycardia has been employed in medical literature for about thirty years to signify a great acceleration of the heart, of sudden onset and equally sudden cessation. At first it was applied rather indiscriminately to a number of conditions of quite different pathology, for the clinical features of the disease were not always sufficiently definite to allow of an accurate diagnosis being made. Indeed, exact definition of the expression was impossible until the mechanism whereby the characteristic attacks were produced was fully understood. It is now generally recognized that the term should be restricted to cases of rapid and regular tachycardia, where the impulse causing contraction arises at some focus other than the sino-auricular node. Theoretically, this focus may be situated in the auricle, ventricle, or in the tissues uniting them, and cases of this condition thus fall into one of three groups according to their origin, whether auricular, ventricular, or nodal. Clinical instances of all three types have been recorded, but whereas examples of the auricular variety are not uncommon those of the other two are extremely rare.

In two of the cases described here the ectopic focus lay in the auricle, in one in the ventricle, and in the last either in the auricle or junctional tissues.

Our knowledge of the morbid anatomy of paroxysmal tachycardia is still very scanty, since in only a few cases have microscopic sections of the heart muscle been examined, and much more evidence is needed before we can co-relate the site of ectopic impulse formation with the position of the lesion in the heart muscle.

One of the objects in investigating these cases was to ascertain how far the diagnosis made from the electro-cardiograms was in agreement with the condition of the heart found histologically.

*Case I.* K. K., a solicitor, aged 45, was admitted on June 22, 1913, into Guy's Hospital under the care of Dr. Newton Pitt.

For some years previously he had been subject to cough during the winter months, but otherwise he had been a healthy man. He had always been temperate in his habits, and his appearance did not suggest chronic alcoholism. There was no history of rheumatism. Syphilis was denied and the Wassermann reaction was negative.

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In December, 1912, he began to suffer from attacks of praecordial pain, which he ascribed to indigestion; these attacks gradually became more frequent and more severe, and towards the end of January began to be associated with some dyspnoea.

He sought medical advice, and was confined to bed for five weeks. His condition improved with rest, and he returned to his work and continued it for 2½ months. In June the same symptoms recurred, and in addition his feet and legs became oedematous.

On admission he was found to be a well-nourished man. He was slightly dyspnoeic, but in no great respiratory distress, and there was no cyanosis. The legs and body were oedematous, as high as the costal margin. The pulse was irregular but of good volume; the artery was not thickened and the systolic arterial pressure was equal to 110 mm. Hg.

The cardiac impulse was diffuse, the deep dullness extended to a point 1½ inches outside the mid-clavicular line, and 1 inch to the right of the sternal margin. The heart sounds were normal. Bubbling râles and rhonchi were heard at both bases. The edge of the liver was palpable 1 inch below the costal margin, and there was some free fluid present in the abdomen. At first the pulse remained irregular, the average rate being 120, but on the twelfth day after admission it suddenly rose to 150 and became quite regular in rhythm. At the same time the patient became rather restless and more dyspnoeic, but otherwise there was no marked alteration in his condition.

The pulse continued regular, and the rate showed little alteration for four days, but on the morning of the sixteenth day it fell to 135, the rhythm remaining regular and the patient felt distinctly better.

Subsequently, however, he became worse and died on July 18. During the last ten days he was too ill to be moved for electro-cardiographic examination, but it was noticed that the heart was sometimes fast and regular and at other times slower and irregular.

#### *Description of Electro-cardiograms.*

For purposes of description it is most convenient to examine the electro-cardiograms in the following order: (1) those corresponding to the normal rhythm; (2) those in which normal cycles are associated with extra-systoles; (3) those of the periods of tachycardia.

*The normal rhythm* (Figs. 1, 2, and 3). These curves were taken on the sixteenth day, a short time after the paroxysm had ceased. The auricular contraction is represented in all three figures, but P is inverted in Fig. 1. The ventricular complexes represent beats of supraventricular origin. In Fig. 1 R is well marked and T is inverted; in Fig. 2 R is short, S is present, and T is not inverted; in Fig. 3 R is again short, S is deep, and T is not inverted. The P-R interval is 0.13 sec. Normal cycles and extra-systoles are shown in Figs. 4, 5, and 6.

In Fig. 4 two normal cycles are shown at A<sup>1</sup> and A<sup>2</sup>, which are similar in form to those of the normal rhythm except that P is upright and the P-R interval is lengthened. The second of these is succeeded by an extra-systole x<sup>1</sup> consisting of a Q, R, S complex and an upright T; a compensatory pause follows, terminated by a normal cycle, A<sup>3</sup>. This, in its turn, is followed by two extra-systoles, x<sup>3</sup> and x<sup>4</sup>, a compensatory pause and a normal cycle, A<sup>4</sup>.

Similar events are shown in Fig. 5. The figure starts with two normal cycles,  $A^1, A^2$ , which are precisely similar to those of the normal rhythm; then follow three extra-systoles,  $x^1, x^2, x^3$ , a compensatory pause, and another normal cycle,  $A^3$ . This last cycle is succeeded by four extra-systoles,  $x^4, x^5, x^6, x^7$ . The sequence of events is not so clear in Fig. 6, since the auricular representatives are not shown. Ventricular complexes similar to those of the normal rhythm are shown at  $A^1, A^2, A^3$ . The cycle  $A^1$  is followed by three extra-systoles,  $x^1, x^2, x^3$ , and a compensatory pause; the cycle  $A^2$  is followed by four extra-systoles,  $x^4, x^5, x^6, x^7$ , and a compensatory pause. The auricular rhythm during the extra-systoles is undisturbed; that this is the case is best seen in Fig. 5. The interval between the two auricular waves,  $p^1, p^2$ , of the first two normal cycles is 0.52 sec.; the third auricular wave,  $p^3$ , is seen 0.52 sec. later, occurring just before the first extra-systole. The two succeeding auricular waves,  $p^4$  and  $p^5$ , can be distinguished after equal intervals, falling upon and modifying the shape of the T waves of the second and third extra-systoles. Finally, the auricular wave,  $p^6$ , belonging to the normal cycle  $A^3$  is seen at the expected point, and is followed by four more,  $p^7, p^8, p^9$ , and  $p^{10}$ , at equal intervals. The fact that the auricular rhythm is undisturbed shows that these extra-systoles are not auricular in origin. Further, the form of the extra-systoles differs from that of beats of supraventricular origin. These two facts make it clear that these beats have been excited from some point in one or other ventricle and that the extra-systoles are ventricular.

*The Electro-cardiograms of the Long Paroxysms (Figs. 7, 8, and 9).*

An examination of the electro-cardiograms taken during the long paroxysms shows that the complexes in all three leads are almost exactly similar in form to those of the extra-systoles in the corresponding leads in Figs. 4, 5, and 6. It has been pointed out that these arose in the ventricle, and hence it is reasonable to conclude that all the beats of the paroxysm have the same origin, and that this is a true ventricular tachycardia similar to those which Lewis produced in dogs.

The auricular representatives are rather difficult to disentangle; they can be distinguished best in Fig. 8. At the points marked  $p^2$  and  $p^6$  there are waves whose presence can only be explained on the supposition that they are due to contractions of the auricle. At  $p^1$  the form of the extra-systole is modified by the superposition of a wave very similar in form to  $p^2$ . The curve that results is almost identical in shape with that of an extra-systole in the same lead of the last figure ( $x^6$ , Fig. 5); this latter curve consists of a ventricular complex to which an auricular wave has been added, and it seems probable that the same explanation holds good for the shape of the curve in question. The interval between  $p^1$  and  $p^2$  is 0.52 sec. If successive intervals of this length are measured along the curve they fall at the points marked  $p^3, p^4, p^5, p^6$ . At  $p^3$  the height of the first elevation of the complex is increased;

the summit of the second wave of the complex is nearly flat at  $P^4$  instead of being curved, and at  $P^5$  it is pointed as at  $P^1$ . The most probable explanation following on the ventricular complexes is that they are due to the presence of auricular waves, falling on the ventricular complexes.  $P^6$  would then be the sixth auricular wave of the series in question, and would fall at the expected point. It will be noticed that the auricular contractions bear no fixed relation to the ventricular contractions, and from this fact the following conclusions may be drawn: (1) the ventricular contractions are not propagated from the auricle; (2) the auricular and ventricular contractions do not arise from a common centre such as the junctional tissues; (3) the auricular contractions are not propagated from the ventricle, i.e. they are not retrograde.

The maintenance of the normal auricular rhythm is rather remarkable, for Lewis has shown that if ventricular tachycardia is produced experimentally the auricular rhythm is usually disturbed after a short time. This may possibly be explained by the fact that the patient was taking digitalis, and that the conduction between auricle and ventricle was thus impaired.

#### *Post-mortem Examination.*

The autopsy was made nineteen hours after death. The body was that of a well-nourished man. The legs, abdominal wall, and back as high as the costal margin were oedematous, and in the fat covering the abdominal muscles were many small areas of pigmentation probably due to thrombosis. There were firm adhesions over the middle and lower lobes of the right lung and over the apex of the left.

The lungs were moderately emphysematous along the anterior margins, and the bases were tough and engorged. There was a large infarct in each upper lobe. The trachea and bronchi were congested.

The liver was somewhat enlarged and showed advanced nutmeg change. The gall-bladder was natural. The stomach was congested, but the intestines showed no abnormality. The kidneys were of normal size; they were tough in consistence and the vessels were engorged. The spleen was firm. The pancreas and suprarenal capsules showed no abnormality. The brain was not examined. There was considerable atheroma of the aorta, particularly in the abdominal part.

The heart was fixed in formalin. Enlargement was definite, and the weight without the pericardium was  $19\frac{1}{2}$  oz.

The *right* side of the heart was greatly dilated and showed no signs of hypertrophy in either auricle or ventricle. There was a considerable amount of post-mortem clot and the endocardium of both chambers was blood-stained. There were no lesions of the endocardium or the valves, either old or recent.

The *left ventricle* was dilated and hypertrophied. The cavity was filled with a large ante-mortem clot which was firmly adherent over a large area of the left side of the interventricular septum, and extended from the apex of the ventricle to within two inches below the aortic valves. The right and posterior cusps of the aortic valve were thickened at the base, and there was a patch of atheroma on the surface of the aorta about an inch above the valves. Both flaps of the mitral valve were thickened—the right flap markedly so near its base—and on the ventricular surface of the right flap calcification was beginning to be evident. There were no recent lesions of the valves, and the right auricle showed nothing beyond a staining of the endocardium.

The whole of the epicardium was thickened and wrinkled. There was a patch of old pericarditis about four inches square with a shaggy surface. There was no evidence of recent mischief.

Frozen sections were examined for fatty changes in the muscle fibres, but the results from all parts of the heart were negative.

#### *Histological Examination.*

The *right auricle* showed a general increase of connective tissue involving the sino-auricular node as well as the ordinary muscle. There was marked vascular engorgement over the whole of this part of the heart, and a sparse irregularly distributed infiltration of lymphocytes throughout the upper portion of both auricles. There was no evidence of thrombosis in this region.

The lower portion of the auricular musculature in the interauricular septum was normal, except in the neighbourhood of the upper portion of the central fibrous body, where there was a sparse infiltration of lymphocytes—a condition which was also found around the attachment of the cusps of the aortic valve.

The *auriculo-ventricular node and bundle* showed comparatively few changes. A small infiltration of large mononuclear cells was found on the right side of the central fibrous body close to the upper portion of the node, and a few lymphocytic infiltrations were found along the course of the main bundle. In that portion of the bundle found in the fibrous septum there appeared to be a definite increase in the amount of connective tissue. The remainder of the changes of this region were confined to structures other than the node and bundle, and included such conditions as sub-endocardial vascular engorgement in the lowest portions of the auricular muscle and small infiltrations of lymphocytes in the upper portion of the ventricular musculature, none of which were found in close proximity to either branch of the bundle.

The main interest of the case centres round the ante-mortem clot found adhering to the left side of the interventricular septum. Histological examination of this region made it fairly evident that the pathological process was still active at the time of death. All degrees of organization could be found as the area of examination was carried outwards from the septum. The most important change involved two-thirds of the thickness of the interventricular wall, and consisted in a progressive fibrosis, involving the musculature to such an extent that very few cardiac muscle fibres could be recognized as such throughout a considerable amount of tissue. That the process was still active was shown by the large amount of very cellular connective tissue present together with the vascular engorgement accompanied by cellular infiltrations. The result of this process may be summed up briefly as an active conversion of a large portion of the interventricular septum into a vascular connective tissue with an occasional atrophied muscle fibre to be seen here and there. The condition is shown in the microphotograph reproduced in Fig. 15.

The upper portions of the thrombus involved the endocardium over the Purkinje fibres, but there was no definite change in the tissues immediately



round the fibres, only the most superficial layers of the endocardium being affected and those only to a slight degree.

The *pericardium* showed a very definite increase in the amount of fully formed connective tissue. The changes were of long standing, and the outermost portions of the cardiac musculature were affected to some extent by the invasion of connective tissue cells from the visceral pericardium.

*Case II.* The patient, an actor, aged 35, was admitted into Guy's Hospital under the care of Dr. Hale White in September 1912. Nine years before admission he had rheumatic fever, and since that time had been subject to attacks of dyspnoea and praecordial pain. Four days before admission he was suddenly seized with praecordial pain which became so severe that he was brought to hospital.

On admission he was a short, rather wasted man; he complained of severe pain over the heart and was in considerable respiratory distress. His expression was anxious, there was some cyanosis of the lips, and the veins of the neck were engorged and pulsating.

There was some oedema round the ankles and over the sacrum.

The pulse was of small volume and low tension. The rate was 160 and the rhythm regular. The radial artery was not thickened. The cardiac impulse was situated in the fifth space  $\frac{1}{2}$  inch external to the mid-clavicular line; the deep dullness started  $\frac{1}{2}$  inch external to this and extended to a point  $\frac{1}{2}$  inch from the right sternal margin in the fourth space. The heart sounds were faint and there was an apical systolic murmur.

The urine contained a trace of albumin, but the respiratory, alimentary, and nervous systems presented no abnormality.

Digalen, strychnine, and caffeine were injected subcutaneously, but had no effect on the pulse-rate. Subsequently morphia gr.  $\frac{1}{2}$  was given and the patient slept comfortably for some hours; on awaking he felt better, but the pulse-rate was unaltered.

After he had been in hospital three days the pulse abruptly fell to 80. Auscultation now showed the presence of well-marked systolic and pre-systolic murmurs. During the next  $10\frac{1}{2}$  weeks the patient had several attacks of tachycardia; these sometimes caused him much distress and severe vomiting, at other times they were associated with but little discomfort. No drug seemed to have any influence on them, but on one occasion the attack stopped immediately after the application of a poultice to the praecordial area. On January 9 the patient had two attacks, the second of which proved fatal.

Electro-cardiograms were not very easy to obtain, as the patient was a very nervous subject and could not control a tremor which came on whenever he was examined by this method.

The electro-cardiograms from the slow and fast periods are shown in Figs. 10 and 11. In those of the slow period the auricular wave P is well marked; the ventricular complex consists of an upward deviation (R) and a second downward deviation (an inverted T). The ventricular complexes of the fast period are very similar though not quite identical; their shape is that of beats of supraventricular origin, and they may have their point of origin in the junctional tissues or in the auricle. No auricular wave is shown, but it is possible that it was iso-electric, and thus produced no alteration in the tracing. The origin of the ventricular beat, however, was demonstrated by venous pulse-tracings, which showed the



presence of a definite auricular wave. This case, then, is an example of a paroxysmal tachycardia of auricular origin.

The autopsy was performed twelve hours after death. The body was that of a rather small, spare man. There was no oedema. The larynx, trachea, and bronchi looked natural. There were old fibrous adhesions over the pleurae. The lungs contained the usual amount of air; they were somewhat tough and congested, but had not reached the stage of red induration.

The mucous membrane of the stomach was somewhat congested; the intestines looked healthy. There were the scars of two old infarcts in the spleen, but the organ was otherwise natural. The wall of the gall-bladder was oedematous. The liver, pancreas, and kidney appeared normal. There was no atheroma of the aorta except for a small patch one inch above the valves. There were some thin fibrous adhesions between the layers of the pericardium and between the parietal pericardium and pleurae on both sides.

The heart was definitely enlarged and weighed 15 oz. without the pericardium.

Both auricles were considerably dilated. The left ventricle showed both dilatation and hypertrophy, while the right showed very little evidence of hypertrophy.

There was no macroscopic evidence of fatty change anywhere in the walls of the heart chambers, and no evidence of calcareous change or atheroma beyond a thin roughened patch in the right side of the aorta about an inch above the valve cusps.

The two flaps of the *mitral valve* were united, leaving only a narrow elliptical opening between them. The flaps were thickened and there were a few recent fibrinous vegetations near the margins of the opening. No other valvular lesions were present, and the remainder of the endocardium was smooth but thickened, particularly down the left side of the heart.

There were no ante-mortem clots and no macroscopic vascular lesions.

#### *Histological Examination.*

The histological examination was carried out by the cutting of serial sections throughout the extent of the sino-auricular node and the auriculo-ventricular node and bundle. Separate pieces were also removed from the walls of each of the chambers of the heart. Examination for fatty changes in the muscle was carried out by means of frozen sections, but the result in every instance was negative.

The *auricular musculature* appeared to be normal, and there was nothing in the appearance of the muscle fibres themselves which could be described as the manifestation of a pathological change. There was no undue amount of connective tissue, the vessels were normal, and the only part of the musculature involved in the changes described below was a narrow strip immediately under the pericardium on the anterior wall of the auricle.

In the region of the *sino-auricular node* there were a considerable number of pathological changes. There were lymphocytic infiltrations—for the most part perivascular—all the way down the anterior surface of the auricle in the fatty tissue between the musculature and the pericardium. In two places there were definite extravasations of red blood cells, and one of the haemorrhages was in

immediate relationship with the right side of the node. The infiltrations were densest in the neighbourhood of the upper portion of the node, and tended to become less marked towards the region of the auricular appendix.

In the node itself there appeared to be a definite increase in the amount of collagenous fibrous tissue in the immediate neighbourhood of the main artery of supply, but this did not involve the great bulk of the nodal tissue. There were several perivascular infiltrations of large mononuclear cells encroaching on the nodal substance on the right side, and a typical example of these is shown in the microphotograph reproduced in Fig. 16. In going through the series of sections some of the smaller vessels showed a well-marked prominence of the lining endothelium. There was nothing in the appearance of the nodal muscle fibres which calls for comment.

The *auriculo-ventricular node and bundle* showed no change as regards the muscle fibres themselves. There was an increase of coarse connective tissue in the lower portion of the node and close to the central fibrous body, but this was quite localized. The central fibrous body was apparently the seat of an inflammatory process, evidenced by the proliferation of the constituents of the small vessels and small perivascular infiltrations of lymphocytes and large mononuclear cells scattered throughout this particular part of the heart. Some of these infiltrations encroached on the nodal tissue at its margin, but there was no discernible alteration in the muscle fibres at this spot. At the posterior end of the node there was an excess of fatty tissue, but there was no evidence of atrophy or any other change in the fibres. There were a few scattered lymphocytes here and there throughout the node and bundle. The continuity of the latter structure was uninterrupted in both its branches.

The *endocardium* all down the left side of the heart was thickened—in places forming a layer of dense fibrous tissue an eighth of an inch thick. The vessels underlying this thickened endocardium were hyperplastic and in some cases were surrounded by small infiltrations. The appearances suggested a chronic inflammation which was still active. The valves, with the exception of the mitral, were all quite normal. This particular valve showed a fibrosis of very long standing and a few recent vegetations near the margin of the slit-like opening between the edges of the two adherent flaps.

The *vessels* throughout the heart showed no sign of thrombosis and, apart from those described in connexion with the endocardium of the left side, showed an irregularly distributed condition of inflammation evidenced by prominent endothelium and sharply outlined perivascular lymphatic spaces. In a few cases the adventitia was thickened, and one or two of the main arteries of the septum showed an extraordinarily small lumen as compared with the thickness of the walls. Part of this last condition was certainly due to an endarteritis.

The musculature in both auricles and ventricles showed no changes. There was no undue amount of connective tissue, and no fatty changes could be demonstrated by histological methods.

*Case III.* The patient, a woman, aged 57, was admitted into Guy's Hospital under the care of Dr. Fawcett in August, 1913. She was married and had had two children.

She gave no history of rheumatism or chorea; the Wassermann reaction was negative. She said she only took a moderate amount of beer, but had been treated for peripheral neuritis, which was ascribed to alcohol. For ten years she had suffered from dyspnoea and praecordial pain, and in September, 1912, was treated in hospital for cardiac failure. In July, 1913, her symptoms became more severe, and she noticed in addition that her legs were swelling.

On admission she was a stout woman; she was very dyspnoeic, but was not cyanosed. Both the legs and the abdominal wall were oedematous. The pulse was irregular, the rate was 76, and the radial artery was not thickened.

The cardiac impulse was diffuse, and the deep dullness extended to a point  $1\frac{1}{2}$  inches external to the mid-clavicular line and 1 inch to the right of the sternal margin. There was a soft systolic murmur in the mitral area. The abdomen contained free fluid. The liver was not palpable.

There were no abnormal physical signs in the lungs, and the urine did not contain albumin. Venesection was at once performed and afforded some relief. She was given a mixture containing tincture of digitalis (5i per diem), but this was omitted after ten days because the patient started to vomit, and strophanthone (Qxliv per diem) was substituted. A fortnight after admission the pulse suddenly rose to 160 and became quite regular; at the same time the patient's general condition became worse and she suffered from severe vomiting and diarrhoea. The attack lasted three days and the pulse then became slower and irregular again and the vomiting ceased. Two days later she had another attack which lasted five days; this attack was also associated with vomiting and much flatulence.

She died suddenly three days after the second attack; just before death the pulse was fast and regular.

Unfortunately the analysis of the case is incomplete, since only a single electro-cardiogram was taken, and legible jugular tracings could not be obtained owing to the patient's restlessness. The electro-cardiogram which was taken during the paroxysm is shown in Fig. 12.

It shows a series of ventricular complexes, consisting of a tall R and a partially inverted T. No representative of the auricular contraction is seen; it is possible, however, that P is present, but is obscured by one of the other waves.

The beats are clearly of supra-ventricular origin, and the site of impulse formation may have been in the auricle or in the junctional tissues, but without further evidence it is impossible to decide this point.

Permission was obtained to examine the heart only.

The heart was fixed in formalin. It was distinctly enlarged and weighed without the pericardium 20 oz. There was a definite increase in the amount of epicardial fat.

The *right ventricle* was hypertrophied and dilated. There was a large ante-mortem clot, moulded, but not adherent to the endocardium, which extended through the pulmonary orifice into both branches of the pulmonary artery (Fig. 17). The more recent depositions of fibrin were in the arterial portion of the clot and the process was still active at the time of death. It was not attached to any portion of the pulmonary valve.

The *left ventricle* was hypertrophied and showed a small amount of dilatation. There was no thrombosis and the endocardium was smooth with small thickened patches here and there. The flaps of the mitral valve showed thickened fibrous plaques at their edges, but no calcareous changes and no recent mischief. The *aortic valves* were normal, and the only valvular lesion found in the heart was that in the mitral. Both the *auricles* were dilated and

the endocardial surface showed post-mortem blood-staining in each case, but there was no evidence of thrombosis.

The *ventricular muscle* throughout the heart was paler than normal, and examination by means of frozen sections showed the presence of a definite degree of fatty degeneration, together with a certain amount of fibrosis.

#### *Histological Examination.*

The sino-auricular node and the upper part of the heart were the only situations where anything definitely abnormal could be found. The manifestation of a morbid process at work consisted of a series of lymphocytic infiltrations mainly around the upper portion of the sino-auricular node.

These infiltrations were entirely perivascular, and consisted almost entirely of small lymphocytes with an occasional large mononuclear cell. A typical example is shown in the microphotograph reproduced in Fig. 18. As regards the remainder of the upper part of the heart, the changes were confined to a few small perivascular infiltrations in the region of the coronary sinus. The left auricle was normal, and there were a few scattered lymphocytes here and there in the interauricular septum above the *a.-v.* node. There was a fair amount of perivascular fibrosis throughout the entire heart, and the condition of the vessels in the upper part differed in no respect from that of the vessels of the heart in general.

The *auriculo-ventricular node and bundle* were apparently unaffected, and the only changes observed in connexion with these structures were perivascular fibrosis with a few lymphocytes scattered here and there among the connective tissue.

The *vessels* showed, in the case of the larger arterioles, a definite increase of fully formed connective tissue in the adventitial coat. The smaller vessels showed an increase of cellular connective tissue unaccompanied in the majority of cases by cellular infiltrations, with the exception of those in the upper part of the heart described above in connexion with the sino-auricular node and the adjacent structures.

The *valves* were normal with the exception of the mitral flaps, which showed an old sclerotic condition near their margins.

The pericardium showed no abnormality beyond an increased amount of fat, which showed a tendency to infiltrate the muscle, particularly in the wall of the right ventricle.

*Case IV.* The patient was a married woman, aged 33. She was under the care of Dr. Fawcett, who has kindly allowed us to make use of his clinical notes of the case.

She had scarlet fever when twelve years of age, but gave no history of rheumatism. Her health had been good until the summer of 1910, when she began to suffer from shortness of breath on exertion and attacks of palpitation. These attacks started quite abruptly, usually with a sensation of abdominal discomfort, and terminated suddenly; they varied in duration from fifteen minutes to thirty-six hours; the shorter ones did not cause her very great

distress, but she became very exhausted towards the end of the longer ones. The patient could sometimes stop an attack by lying down and applying a tight abdominal binder.

She never had any oedema, and in the intervals between the attacks enjoyed fairly good health, except for being troubled with some dyspnoea on exertion.

On examination she was a well-nourished woman with a slight flush over the malar bones. She did not complain of any pain or discomfort and was in no respiratory distress.

The pulse was 82, regular in rhythm, and of medium tension; the wall of the artery was not thickened. The heart's apex was in the fifth space, 4 inches from the mid-sternal line; the deep dullness started at the same point and extended  $1\frac{1}{2}$  inches from the mid-sternal line on the right.

There was a rough pre-systolic murmur terminating in a loud first sound. There was no oedema, and the respiratory, alimentary, and nervous systems presented no abnormality. The urine did not contain albumin.

On the occasion when an electro-cardiogram was taken during a paroxysm, she complained of palpitation and slight flatulence, but was able to sit in the chair for examination without much discomfort. She was slightly dyspnoeic, but not cyanosed, although the veins of the neck were rather full. The pulse-rate was 200 and no murmur could be heard on auscultation.

The electro-cardiograms from the slow period (Fig. 13) show a prominent auricular wave P, and a ventricular complex of R and S variations, and a partially inverted T. The P-R interval is 0.17 sec. The ventricular complexes during the paroxysm (Fig. 14) are of similar form, and hence the beats are probably of supra-ventricular origin. No auricular wave appears in the curve, but it is definitely present in a jugular pulse-tracing, and hence the tachycardia is of auricular origin. The a-c interval on the venous curve during the paroxysm is 0.17 sec., which is exactly equal to the P-R interval of the slow periods.

#### *Summary.*

Four cases of paroxysmal tachycardia are described, in three of which the heart was examined histologically.

In the first case the focus from which the ectopic beats arose was diagnosed as being situated in the ventricles. Post mortem, the interventricular septum was the site of the most extensive disease.

In the second and third cases the tachycardia was supraventricular in origin, in one case being auricular, in the other, either auricular or nodal. In both these cases the most marked lesions were found in the neighbourhood of the sino-auricular node. The histological examination thus confirms diagnosis made from the electro-cardiograms.

The fourth case was one of auricular origin; in the intervals between the attacks the patient enjoyed fairly good health.

In conclusion, we wish to express our thanks to Dr. Hale White, Dr. Newton Pitt, and Dr. Fawcett for permission to publish these cases.



## EXPLANATION OF FIGURES (PLATES 19-24).

The time-marker in all cases indicates  $\frac{1}{2}$  second.

FIGS. 1, 2, and 3 curves taken in Case I while the rhythm was normal. In Fig. 1 the leads are from right and left arms; in Fig. 2 from right arm and left leg; in Fig. 3 from left arm and left leg.

FIGS. 4, 5, and 6. Curves taken in Case I, showing normal cycles and extra-systoles. In Fig. 4 the leads are from the right and left arms; in Fig. 5 from right arm and left leg; in Fig. 6 from left arm and left leg.

FIGS. 7, 8, and 9. Curves taken in Case I during a paroxysm. In Fig. 7 the leads are from right and left arms; in Fig. 8 from right arm and left leg; in Fig. 9 from left arm and left leg.

FIG. 10. Curve taken in Case II while the rhythm was normal.

FIG. 11. Curve taken in Case II during a paroxysm.

FIG. 12. Curve in Case III, taken during a paroxysm.

FIG. 13. Curve in Case IV, taken while the rhythm was normal.

FIG. 14. Curve in Case IV, taken during a paroxysm.

FIG. 15. Case I. Microphotograph of interventricular septum.

FIG. 16. Case II. Microphotograph of sino-auricular node.

FIG. 17. Case III. Right ventricle with ante-mortem clot.

FIG. 18. Case III. Microphotograph of sino-auricular node.



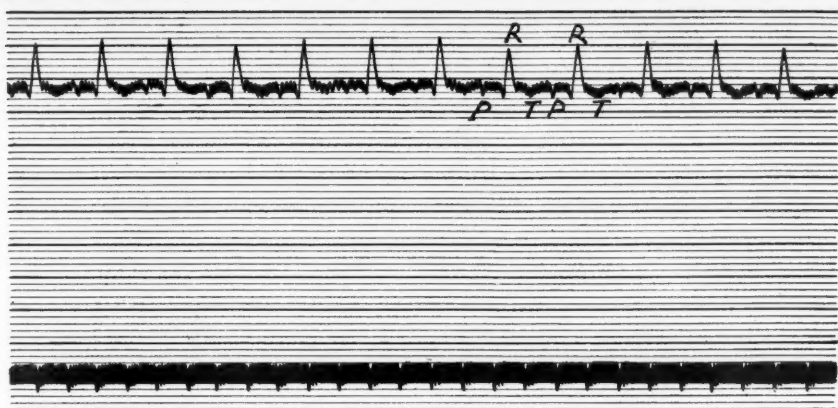


FIG. 1

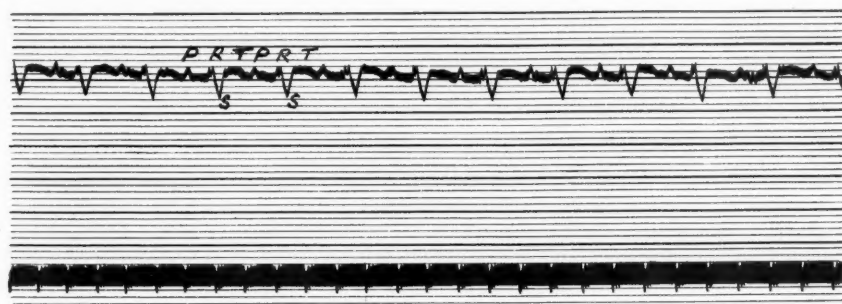


FIG. 2

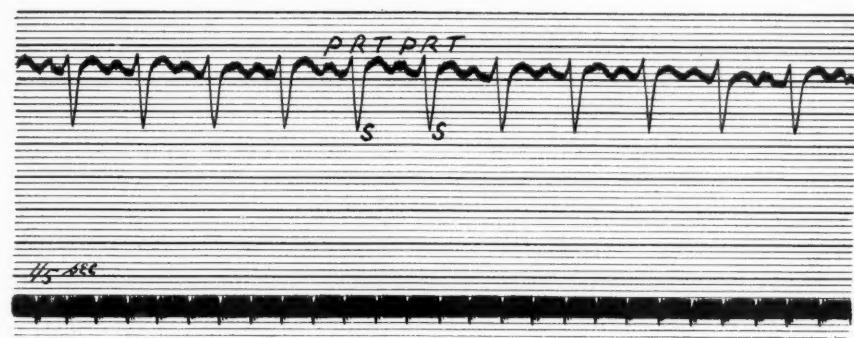


FIG. 3

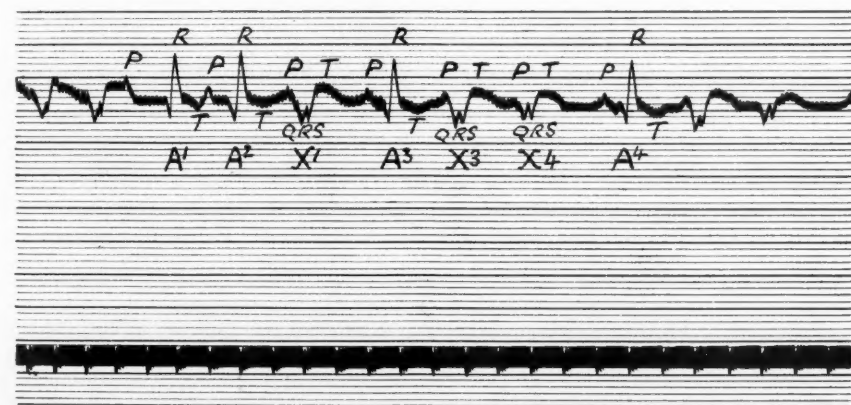
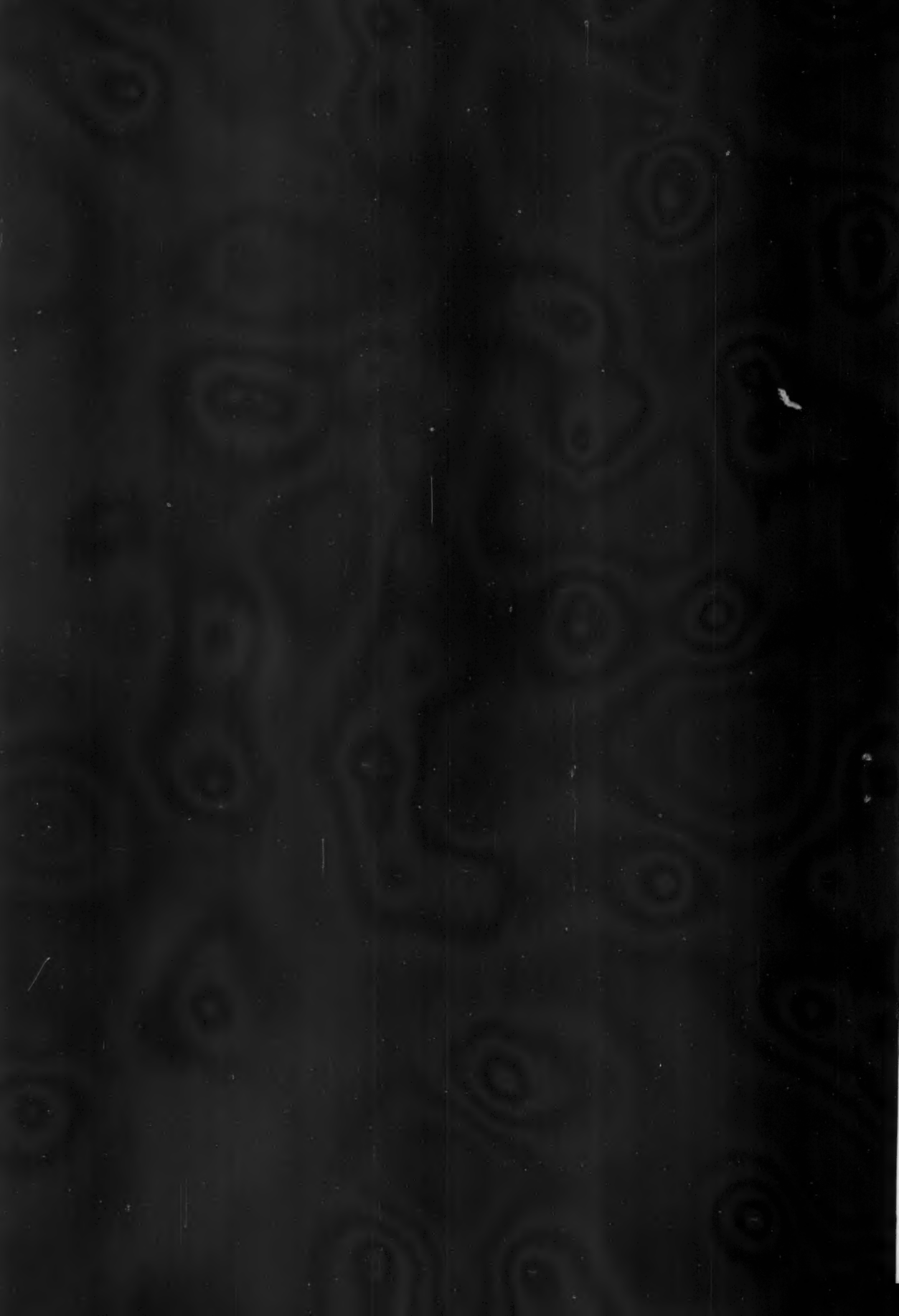


FIG. 4







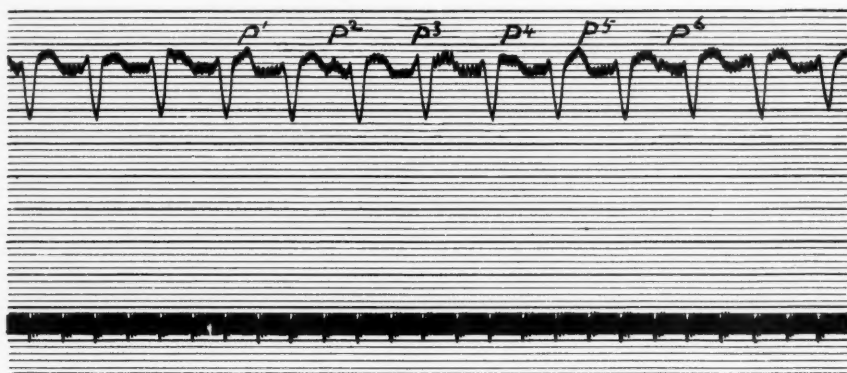


FIG. 8

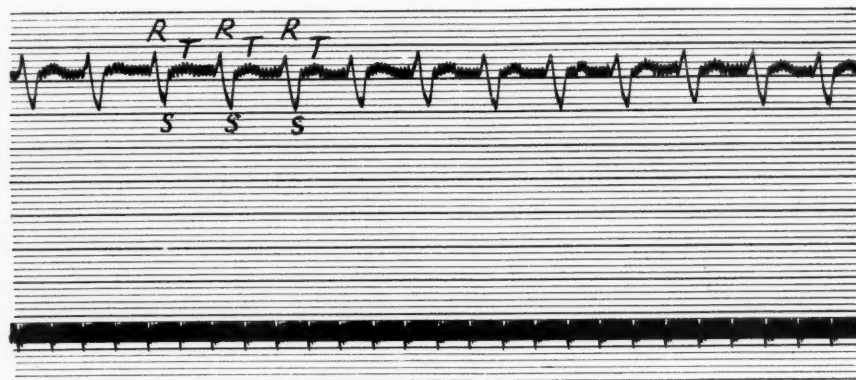


FIG. 9

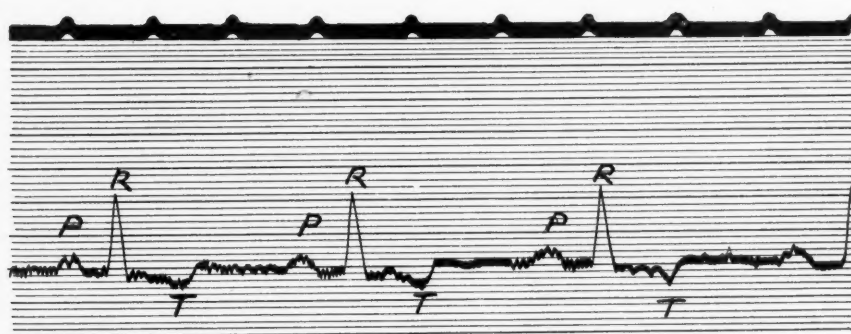


FIG. 10





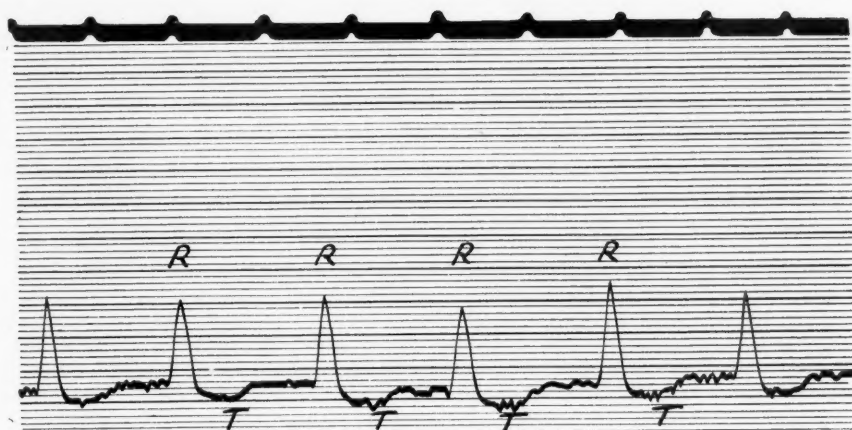


FIG. 11

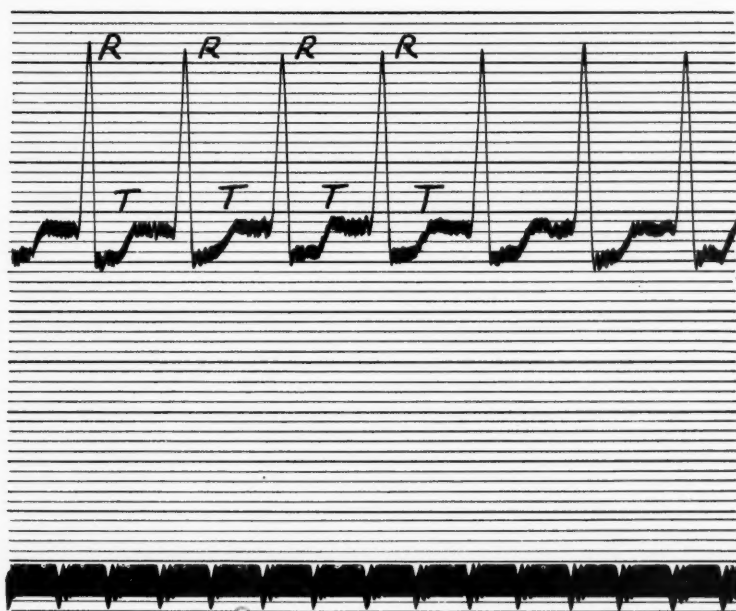


FIG. 12

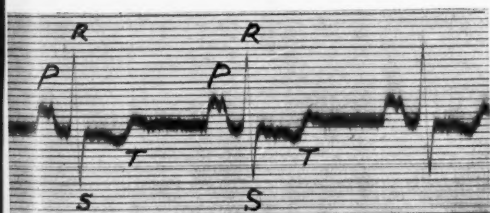


FIG. 13

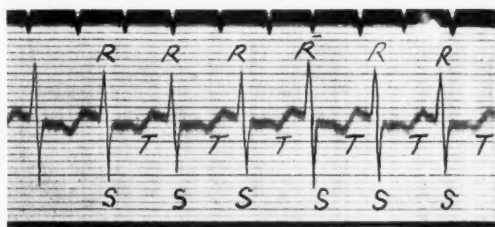


FIG. 14



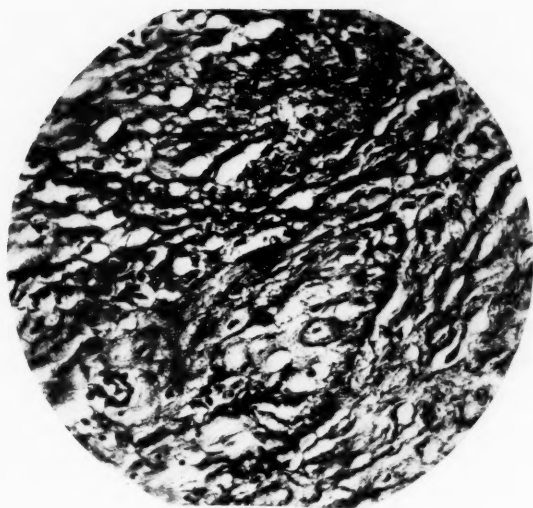


FIG. 15

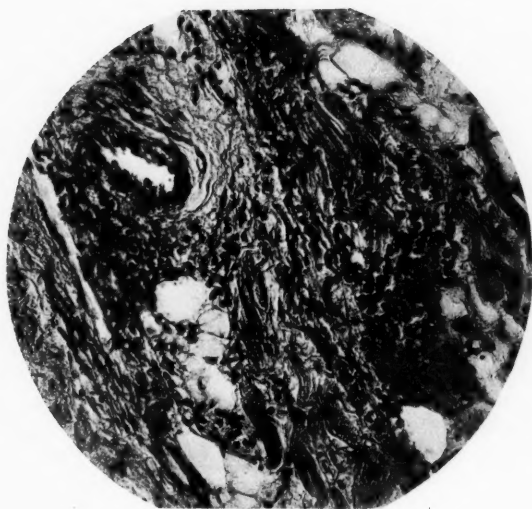


FIG. 16



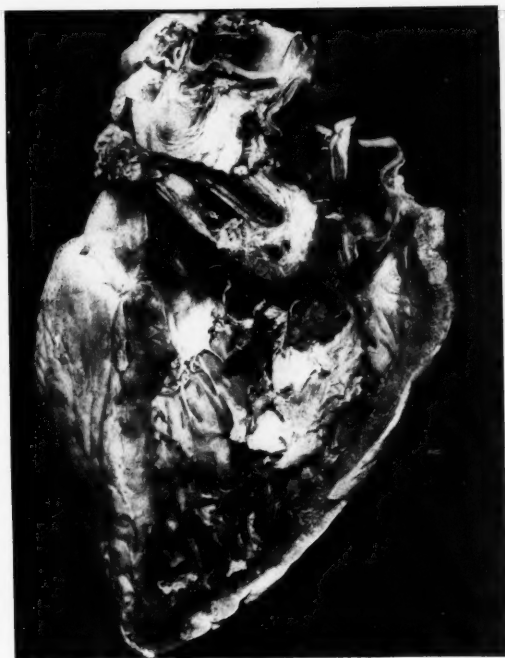


FIG. 17

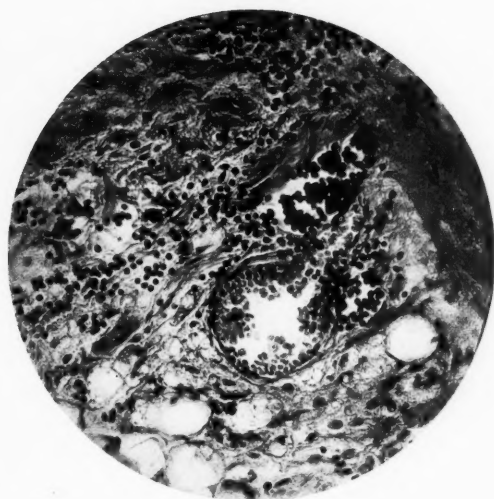


FIG. 18





## CHOLESTERIN: AN ACCOUNT OF ITS RELATIONS TO PATHOLOGY AND PHYSIOLOGY

By J. W. McNEE

(From the Department of Pathology, University of Glasgow)

THE substance cholesterin has in recent years become fairly familiar to medical readers through its connexion with various pathological states, but our knowledge of its function in physiology and of its rôle in certain conditions of disease is still very deficient. In the last few years, however, a number of important points have been elucidated, but the knowledge is so scattered in a variety of papers through the English, French, German, and Russian literature, that few attempts have been made so far to sum up what we know of the relations of cholesterin to the science of medicine. In the succeeding pages a brief account of what research has yielded in this direction will be briefly set down.

In 1907 Craven Moore (35) published a very good description of the facts then known of the chemical, physical, and biological relations of cholesterin to the organism; but all the work dealt with here has appeared since then, a sufficient proof of the interest and rapid advance in our knowledge of cholesterin.

Following investigation of how organs become infiltrated with fat, we came to know that in addition to deposit of the ordinary glycerine or neutral fat there is another fatty change, which consists in the laying down in various organs and tissues of fat-like substances, now identified chemically as cholesterin-esters of the fatty acids. These peculiar fat-like bodies have the curious physical property of being doubly refractive to light when viewed through the crossed prisms of the polariscope. This property had been previously recognized, but was drawn attention to afresh by Kaiserling and Orgler (25), in the case of the suprarenal cortex, the substance being named by them 'myelin', following the old nomenclature of Virchow and F. W. Beneke. Then, by the important work of Panzer (38) and of Aschoff (4) it was shown that these doubly refractive substances consist chemically of nothing else than cholesterin-esters, which can be readily identified whenever they occur in the body by this property.

It was evident at once that these cholesterin-ester fats must have a definite rôle in physiology, since they are found normally in certain of the body tissues, such as the suprarenal cortex, in which a considerable amount of cholesterin-

ester is found. Pathologically, deposits occur in the organs in a great variety of conditions, and these will be referred to in detail in the course of this article.

At first all our knowledge came from the morphological side, and notice must be taken here of the well-known work of Aschoff (5) and his pupil Kawamura (26). Various staining methods were elaborated to distinguish this type of fat from the ordinary neutral fat, among such being the Nile-blue method of Lorrain Smith (45) and the method of Dietrich (16). Our exact knowledge, however, has made great strides since the discovery of a good and efficient chemical method of estimating the amounts of cholesterol and cholesterol-esters in the tissues and body fluids. Such a method we now possess in the digitonin method of Windaus (52), who found that cholesterol unites with the alkaloid digitonin, in alcoholic solutions of the two substances, to form a staple compound digitonin-cholesteride, which precipitates as a white crystalline substance. The union takes place in a definite quantitative proportion, the ratio of cholesterol to digitonin-cholesteride being 1 to 4. By weighing the precipitate the amount of cholesterol in any given tissue is easily determined. Cholesterol-ester cannot be directly estimated as such, but must be first saponified to free the cholesterol. If it is desired to estimate the amounts of cholesterol and cholesterol-ester separately the material must be divided into two parts; in one part the free cholesterol is estimated, in the other the total cholesterol, after setting free by saponification that present as ester. The amount of cholesterol-ester is then readily found by simple subtraction. By means of this method, fuller details of which are given in many of the articles to which reference must be made later on, we owe much of the information we at present possess of the functions of cholesterol in the organism.

We owe to clinicians, especially those of the French school, another kind of method, colorimetric in type, of estimating cholesterol. This type of method is more applicable to the fluids of the body, and by means of it many interesting observations in connexion with the varying cholesterol content of the blood-serum have been made. Such colorimetric methods have been published by Grigaut (20) and Iscovesco (24) in France; Weston and Kent (49) in America; and lately in Germany Autenrieth and Funk (9) have applied the well-known Königsberger-Autenrieth colorimeter to the detection of cholesterol. This latter apparatus and the method of Weston and Kent have in the author's hands yielded very good and uniform results, when controlled by the Windaus method. The colour test is that of Liebermann, and is as follows: When to a solution containing cholesterol, anhydrous acetic acid and a few drops of concentrated sulphuric acid are added, a bright green colour results. This colour is compared either with a standard green solution, as when the Königsberger-Autenrieth colorimeter is used, or with solutions of known strength of pure cholesterol to which anhydrous acetic acid and sulphuric acid were also added. Such, then, are the chief methods at our disposal for estimating cholesterol quantitatively.

Now cholesterol, as has long been known, is a constant constituent of every cell in the body. In the cells of certain tissues it is exceedingly abundant, as in

the white matter of the central nervous system and in the cells of the suprarenal cortex. In the blood-serum it is present in considerable amount, and also in the bile. In the blood-serum it circulates chiefly as cholesterin-ester, only a small amount normally being free; on the contrary, in the bile cholesterin-ester is often merely present in traces, or may be absent, the bulk of the cholesterin being free.

We shall see later on that experimental work has suggested the existence of a definite metabolic circulation of cholesterin in the body, of a conservative nature, but how it is controlled and what are its functions is as yet not clear.

As has been the case on numerous occasions in other departments of medicine, it is a study of the pathological changes with which cholesterin has to do that has given us much of the knowledge we possess of its relations to physiology. Thus it will be better if we proceed to discuss first of all the pathological changes in the organs in which cholesterin is concerned and the variations in the cholesterin content of the body-fluids in disease.

Deposits of cholesterin-ester have been found in numerous pathological states. They occur in the arteries in arterio-sclerosis, in the kidneys in chronic Bright's disease (granular contracted kidney), in the Fallopian tubes in chronic inflammations, in malignant tumours (Powell White (50)), in the cells of that somewhat uncommon skin condition xanthoma or xanthelasma, in the retina to form the well-known 'white spots' in Bright's disease and diabetes, &c.; also one type of gall-stone, the so-called 'solitary stone', is composed of pure cholesterin. This is not given as a full list, but is only to show at the outset with what a wide field of pathology cholesterin is concerned.

#### *Changes in the Cholesterin Content of the Blood-Serum.*

The changes in the cholesterin content of the serum in disease have now been investigated by quite a number of observers, e. g. Grigaut (20), Iscovesco (24), Defaye (15), Klinkert (28), Weston and Kent (49), Bacmeister and Henes (10), &c. Much very interesting information has already been collected, and some of the changes are really very curious. What the reason of the changes is we have as yet no definite idea.

Most of the work on the blood-serum has been carried out in the wards by means of the various colorimetric methods already referred to, but the findings have been controlled both by Klinkert and by the author with the Windaus method, and the results correspond very well. As a rule a slightly lower reading is given by the colorimetric than by the chemical method.

The normal cholesterin content of the blood-serum seems to be about 1.5 to 1.8 mg. per 1 c.c. serum, i. e. about 0.015 to 0.018 per cent. Klinkert gives a series of cases, seventeen in number, in which both the Grigaut and Windaus methods were used simultaneously. His average figure by the colorimetric method was 1.795 gm. per litre (i. e. 0.0176 per cent.); and by the Windaus method 1.822 gm. per litre (i. e. 0.0182 per cent.). Bacmeister and Henes, in a series of

nine normal cases tested by the Weston and Kent method, found an average of 1.48 grm. per litre (i. e. about 0.15 per cent.).

The figure 1.5 to 1.8 grm. per litre represents, of course, the *total* cholesterin of the serum, the cholesterin-ester being always saponified to liberate the cholesterin. The changes in diseased conditions are both quantitative and qualitative, but especially the former. A marked increase in the cholesterin in the serum is found almost constantly in cases of arterio-sclerosis, in chronic Bright's disease, in jaundice, in diabetes mellitus, in xanthoma (xanthelasma), and always in pregnancy. There is a decreased cholesterin content in almost all febrile diseases (with the notable exception of enteric fever), in tuberculosis, and in old age. As to qualitative changes, Widal, Weil, and Laudet (51) have found that in jaundice a marked change in the proportions of cholesterin and cholesterin-ester occurs. Whereas normally cholesterin-ester is much the larger part, in jaundice a great increase in the free cholesterin takes place. It is sufficient here merely to direct attention to the fact that in the bile excreted by the liver the cholesterin is nearly all free, only a very small amount being combined as ester.

The changes in the whole cholesterin metabolism in *pregnancy* are of so remarkable a nature, that the changes in the blood-serum will be considered along with the other unusual features in a separate paragraph.

In *chronic Bright's disease* the increase of cholesterin in the serum is, as a rule, very considerable. Klinkert (28) gives a series of eight cases, and the accompanying table is modified from the one given by him.

*Cases of Chronic Interstitial and Parenchymatous Nephritis.*

1. Arterio-sclerotic contracted kidney. . . . .	2.365	grammes per 1,000.
2. Chronic parenchymatous nephritis. . . . .	2.660	
3. " nephritis. Albuminuric retinitis . . . . .	3.910	
4. " parenchymatous nephritis. . . . .	4.260	
5. " nephritis. Albuminuric retinitis . . . . .	2.685	
6. " " Pregnancy . . . . .	3.985	
7. " " " . . . . .	2.710	
8. " " Albuminuric retinitis . . . . .	2.980	

Klinkert also examined four cases of *eclampsia*, in all of which the cholesterin content of the serum was increased, the figures being 2.760, 3.315, 2.740, and 3.210 grm. per litre. The interest in the increased cholesterin content of the serum in nephritis and eclampsia is heightened when certain other manifestations of these diseases are considered. Lauber and Adamük (31) have shown that the peculiar white spots which appear on the retina in early cases of nephritis consist of a deposit of fat, and of *cholesterin fat*. Ginsberg (19) and Chauffard (12) have confirmed this finding. These white retinal spots appear also in eclampsia and disappear when the cholesterin content returns to normal, as will afterwards be referred to. Of great interest, too, in connexion with the increased cholesterin content of the serum (hypercholesterinaemia) in chronic nephritis, and in *arterio-sclerosis*, where a constant increase is also found, are the chemical findings of

Windaus in the analysis of aortae from cases of arterio-sclerosis. The following table from Windaus (53) shows the results of his analyses :

1. *Normal Aortae.*

Free Cholesterin.	Cholesterin-ester.
A. 1.19	0.47
B. 1.03	0.32

2. *Arterio-sclerotic Aortae.*

Free Cholesterin.	Cholesterin-ester.
A. 4.49	3.75
B. 7.41	10.53
C. 6.73	7.92

The figures indicate grammes per 1,000.

Further, Marie and Laroche (33) have shown that the arcus senilis of the cornea, which is so often associated with vascular changes in old people, is simply a cholesterin-ester infiltration of the cornea. A further point is that xanthoma may appear in the course of nephritis.

Experimental work by Russian authors, which will afterwards be described, where rabbits, after prolonged feeding with cholesterin, develop marked changes in the intima of the aorta very similar to the changes in human arterio-sclerosis, may also be drawn attention to here.

In *diabetes mellitus* the increased cholesterin content of the serum was noted by Fischer (18) so long ago as 1903. The increase appears to be inconstant in moderate cases, but in severe cases hypercholesterinaemia is very marked. This fact was pointed out by Klemperer and Umber (27), and has been controlled and confirmed by Klinkert, using the Windaus method. Klinkert's cases are as follows :

*Diabetes Mellitus.*

(Cholesterin content in grammes per litre.)

1. Glycosuria.	No acidosis or polyuria . . . . .	1.510
2. "	Slight acidosis . . . . .	2.835
3. "	Moderate acidosis . . . . .	3.340
4. "	Very marked acidosis and coma . . . . .	3.500
5. "	Slight acidosis . . . . .	2.415
6. "	Slight acidosis . . . . .	3.610
7. "	Marked acidosis . . . . .	3.580
8. "	Marked acidosis . . . . .	4.965

Manifestations of diabetes of interest, when considered along with the fact of this hypercholesterinaemia, are, first of all, the white spots on the retina, which, as von Noorden (37) has pointed out, may disappear entirely when the diabetes is improved by strict dietary measures. Then the fact that in diabetes xanthoma often occurs is thoroughly well established.

In all forms of *chronic jaundice* the cholesterin content of the serum is



increased considerably, although not so markedly as in nephritis or diabetes. Qualitative changes also occur, as has already been pointed out, the free cholesterin being increased instead of the cholesterin-ester. It is found that in chronic hepatic diseases unaccompanied by a jaundice, such as cirrhosis, and even in carcinoma of the liver, or cholelithiasis without jaundice, no hypercholesterinaemia is evident.

In *xanthoma* or *xanthelasma*, a somewhat uncommon condition, the presence of a hypercholesterinaemia is hinted at by the fact that the condition occurs at times in the course of chronic nephritis, diabetes mellitus, and jaundice. It also occurs fairly frequently in women about the time of the menopause. Apert, Pechery, and Rouillard (3) give analyses of two cases, done by the Grigaut method. In a woman aged 60, with xanthoma of the eyelids, they found 5.30 grm. per litre; in a young woman of 17, with xanthoma of the neck and knees, they found 3.15 grm. per litre. The essential feature of xanthoma is the appearance of lemon-yellow, sharply bounded, small tumours in the skin. They occur most commonly on the eyelids, but are found elsewhere. Microscopically, they are composed of interstitial and endothelial-like cells, filled with fat, which was shown by Pinkus and Pick (40) to be doubly refracting, i.e. to be composed of cholesterin-ester. This finding was confirmed by others, while Chvostek (14) has also paid much attention to the pathology of the condition and its connexion with jaundice. Other points in connexion with the occurrence of xanthoma also require discussion. It appears to be a fact that 70 per cent. (Klinkert) of the cases of xanthoma occurring during jaundice are in females. This reminds one at once of facts connected with gall-stone formation, the relations of which to hypercholesterinaemia in pregnancy will presently be fully entered into. Further, various authors have drawn attention to the connexion of xanthoma with ovarian disturbances. The connexion of the disease with the menopause is well known, and Posner (41) has recorded a remarkable case where marked itching appeared during pregnancy, and was followed subsequently by the development of both xanthoma and icterus.

In *adiposity* an increased cholesterin content of the serum has been pointed out by Bacmeister and Henes (10), and it is evident that there is an abnormal metabolism of fats in them. Further study of these cases is much required.

Having considered now the chief pathological conditions characterized by a hypercholesterinaemia, we may turn to those in which the cholesterin is below the normal (*ypocholesterinaemia*). In all acute febrile processes (exanthemata, pneumonia, &c.), the cholesterin is diminished, with the exception of enteric fever. The same holds good for tuberculosis, malignant tumours, and also for old age. Just before death the cholesterin sinks in many conditions. Those who would attribute to cholesterin a function in connexion with the development of immunity explain the diminished content of the serum as due to the using up of the substance in the combat against the diseased process. But as yet there is not a shred of real evidence supporting the view that cholesterin has such a function in the body.



*The Changes in Pregnancy.*

Numerous observations have now shown that during pregnancy the relations of cholesterol in the organism undergo profound changes. As yet we have no idea what this means, or what purpose it may serve. It is possible that what initiates it directly is some disturbance of ovarian function. Hermann and Neumann (22) were the first to show that during pregnancy the cholesterol content of the serum is increased, and their observations have been abundantly confirmed by Chauffard, Laroche, and Grigaut (13), Klinkert, Schlimpert and Huffmann (42), &c. During the last few months of pregnancy the increase may be considerable, and Klinkert gives figures up to 4.255 grm. per litre. His average for seventeen cases, between the seventh and ninth months, is 2.633 grm. per litre (normal 1.8 grm.). Hermann and Neumann have also shown that following the increase or retention of cholesterol during pregnancy, an elimination occurs during the puerperium. The chief means of excretion is the milk, and it was noted that the hypercholesterinaemia passed off more quickly in women who suckled their own children than in those who did not.

In passing it is of interest here to note that in the blood of the newly-born child there is an amount of cholesterol considerably below the normal adult figure. Klinkert gives seven observations from the blood of the umbilical vein, with an average reading of 1.196 grm. per litre.

The hypercholesterinaemia normally present during pregnancy raises at once the question of whether this may have anything to do with the well-recognized tendency of females to gall-stones. All statistics amply support this tendency of the female sex to cholelithiasis, as the following examples show.

Schwarz (44) gives the following table, the ages given being those at which treatment for gall-stones became necessary.

Years.	23-30.	31-40.	41-50.	51-60.	61-75.	Total.
Female	6	34	31	23	7	101
Male	1	5	16	11	12	45

The statistics given by Schröder (43), from von Recklinghausen's laboratory, are also very striking. At a large number of post-mortem examinations gall-stones were found in 20.6 per cent. of females, and in only 4.4 per cent. of males. In females who had borne children the proportion was ten times greater than in others. Grube and Graff (21) give quite similar proportions; they found gall-stones in 764 women and 176 men, a proportion of about 4.6 : 1.

Until recently we had no knowledge whatever of whether a similar increase of cholesterol takes place in the bile in pregnancy as occurs in the serum. Lately, the author, while working in Professor Aschoff's laboratory in Freiburg, had the opportunity of examining the cholesterol content of the gall-bladder bile in four pregnant women, three of whom died after an abortion, and the other as a result of placenta praevia. Particulars of three of these cases have already been published (34). The cholesterol content was examined by the

Windaus method, and a colorimetric method (Weston-Kent), and the results arrived at by the two methods correspond very well. We know from the work of Peirce (39), who examined the cholesterin content of the gall-bladder bile in a variety of conditions (Windaus method), that the normal figure is about 1.5-1.6 grm. per litre.

In a case of exophthalmic goitre, examined by the author as a control (Windaus method), the cholesterin content of the gall-bladder bile was 1.58 grm. per litre.

The following table gives the figures in grammes per litre found in the four cases of pregnancy, and shows that in the bile also there is a marked increase in cholesterin.

*Cases of Pregnancy.*

Case.	Month of Pregnancy.	Windaus Method.		Weston-Kent Method.
		Free Cholesterin.	Cholesterin-ester.	
1.	4	6.04	0.84	5.89
2.	5	6.80	0.40	6.14
3.	6	—	—	6.60
4.	End of pregnancy (placenta praevia)	6.07	0.30	—

This marked increase of cholesterin in the bile in pregnancy has, the author would submit, a distinct importance in explaining the increased frequency of the occurrence of gall-stones in women. Aschoff and Bacmeister (6) have shown that the older and widely accepted ideas of Naunyn (36), that the origin of all gall-stones is inflammatory, must be given up. These authors have shown that there is a class of gall-stones which arises aseptically. The so-called solitary cholesterin stone, whose mode of origin has again been discussed at length in a recent paper by Aschoff (7), belongs to this category. It arises in an aseptic gall-bladder and, as Aschoff would point out, is a sequel to an increased amount of cholesterin in the bile. Such an increase occurs, as we have shown, in pregnancy as an apparently constant phenomenon.

One case seen by the author in Aschoff's laboratory is of considerable interest in this connexion. At the post mortem on a woman, aged 26 years, who had borne two children, a pure cholesterin stone somewhat larger than a pea was found in an otherwise normal gall-bladder. The bile, which was very fluid, gave by the Weston-Kent method the exceedingly large amount of 12.50 grm. of cholesterin per litre.

As to why these extraordinary alterations in the metabolism of cholesterin should occur in pregnancy we are still in the dark. It seems likely, from what we know in other conditions, that the function of the ovary has something to do with its causation, but that brings us no nearer the reason for it occurring at all.

The suprarenal bodies, as Albrecht and Weltmann (1) and Landau (30) have shown, also share in the unusual retention of lipoids in pregnancy, the cells of the cortex becoming laden with cholesterin-ester. This was the case in all the four cases where the bile was investigated by the author.

*The Cholesterin of the Bile.*

The changes in the bile in pregnancy lead us to discuss here the normal cholesterin of the bile, and its changes in pathological states, so far as they are known to us.

It has already been stated that in the bile the greater part of the cholesterin is free, ester only being present in small amount. How is it that the cholesterin, which is directly derived from the cholesterin-ester of the blood-serum, becomes free in its passage through the liver? This point has already attracted attention, and a search has been made by several observers for an enzyme in the liver which splits cholesterin-ester. So far no definite conclusions have been arrived at.

That any increase in the cholesterin content of the serum is followed at once by an increase of cholesterin in the bile is shown by the experiments of Kusumoto (29) and of the author, when taken together. Kusumoto showed in dogs with biliary fistulae that when he injected toluylendiamin to produce haemolysis, an increase in the cholesterin content of the bile rapidly followed. The author in the course of some experiments on dogs, in which toluylendiamin was being injected to induce a haemolytic jaundice, took the opportunity of noting the alterations in the amount of cholesterin in the serum which followed the blood destruction. These results have already been published in part elsewhere (8), so the protocol of only one experiment, which lasted twenty-two days, is now given below.

## EXPERIMENT.

(The dog received in all 4.1 grm. of toluylendiamin in five doses during the experiment.)

Day.	Cholesterin in grammes per litre.
1	0.06
4	0.069
7	0.70
10	1.04
12	1.20
18	3.44
22	1.91

Our knowledge of alterations in the amount of cholesterin in the bile in pathological states is rather scanty. Bacmeister (11) made observations on a case of diabetes, in which a complete biliary fistula existed following an operation, and found the cholesterin was above the normal in amount. Peirce (39), who examined the gall-bladder bile in widely separated pathological conditions, found very high figures in cases of chronic Bright's disease.

All the facts go to show that any increase in the cholesterin content of the blood-serum means an increase in the cholesterin of the bile as well.

*Experimental Work with Cholesterin.*

This may be divided into that undertaken purely with the object of clearing up the normal metabolism and rôle of cholesterin in physiology, and that with the object of throwing light on the various pathological conditions with which cholesterin has to do.

In the former group the most important work from the purely experimental side is that of English authors, Dorée, Ellis, Fraser, and Gardner (17), which has been published in the *Proceedings of the Royal Society of London*, in a series of articles entitled 'The Origin and Destiny of Cholesterol in the Animal Organism'.

From their earlier work they were able to formulate the following hypothesis with regard to the destiny of cholesterin in the organism, namely, that 'Cholesterol is a constituent constantly present in all cells, and when these cells are broken down in the life process the cholesterol is not excreted as a waste product, but is utilized in the formation of new cells. A function of the liver is to break down dead cells, e.g. blood corpuscles, and eliminate their cholesterol in the bile. After the bile has been poured into the intestine in the process of digestion, the cholesterol is reabsorbed, possibly in the form of esters, along with the bile salts, and is carried in the blood-stream to the various centres and tissues for re-incorporation into the constitution of new cells.'

Their later work has chiefly been with a view of supporting this hypothesis, and is highly interesting. They find that feeding rabbits on bran, extracted with ether to remove fats, and to which an excess of cholesterin has been added, leads to an increased absorption of cholesterin into the body, and both the cholesterin and cholesterin-ester content of the blood-serum become increased. Further, the livers of such animals show an increase of total cholesterin far above the normal. Thus the cholesterin content of the blood and liver are in definite relationship to the cholesterin content of the food. In animals kept in a state of inanition, and therefore living on their own tissues, various interesting points arise. A similar storing up of cholesterin in the liver occurs as in the animals fed on a diet rich in cholesterin, and the amount in the blood is also increased. In inanition, too, the kidneys furnish a point of great interest. A diet rich in cholesterin has in rabbits no effect whatever on the cholesterin content of these organs, but during inanition a remarkable accumulation of cholesterin, and especially of cholesterin-ester, occurs. For instance, they found the average cholesterin content of the kidneys of two starved rabbits to be 0.5211 per cent. (0.3937 per cent. free, and 0.1274 per cent. ester), whereas in normal animals figures of 0.2466 per cent. free and 0.0596 per cent. ester were found. The increase during starvation, especially of ester, is thus marked, and these high ester values recall the high ester figures found by Windaus (54) in the kidneys, in pathological conditions such as granular contracted kidneys, &c. No reasonable explanation can be given for such an accumulation of cholesterin-ester in the kidneys.

An interesting account is given by the same authors of observations on

a man whose excretion of cholesterin was examined while he was receiving different diets. They found in their observations on this man, a healthy subject of 39, that the amount of cholesterin excreted in the faeces could all be accounted for, so long as the body weight remained constant, by what was taken in the food. (In man cholesterin appears in the faeces in the form of coprosterol.) During the experiment the man developed an attack of influenza, which resulted in a rapid loss of weight, and during this period the excretion of cholesterin considerably exceeded the intake. This is a remarkable control of the inanition experiments on rabbits.

Turning now to what may be termed the experimental pathology of cholesterin, a considerable amount of work must be drawn attention to. The chief and earliest work in this direction has come from Russian authors. Ignatowski (1908) (23) was the first to make observations on rabbits as to the effect of substituting a purely animal food, and especially animal albumins, for the normal vegetable food. He used ox flesh, eggs, and milk, and carried out experiments of 21 to 198 days' duration. He found morphological changes in the wall of the aorta and in the liver similar to those which will be described immediately. Starakadowski (46) controlled these experiments, using egg-yolk as his diet, and found the same aortic lesions in his rabbits. The changes affected the intima of the aorta, and resembled closely those found in human arterio-sclerosis. These seem to be the first genuine intimal changes which have been produced experimentally in animals. Lubarsch (32) had previously described marked aortic changes, but affecting the media, which he induced by feeding rabbits on a richly animal diet. Stuckey (1910) (47) used meat-juice, egg-white, egg-yolk, and milk in a series of experiments to see which of these had most, if any, effect. He found that whereas meat-juice, egg-white, and milk had scarcely any damaging effect on the aorta, egg-yolk induced a remarkable intimal change. The intima became the seat of marked proliferation and hypertrophy, and infiltration of the hypertrophied area with fat occurred. Pursuing this further, Stuckey sought to find what constituent of the egg-yolk was active in bringing about the change. It seemed *a priori* probable that the albumin fraction had nothing to do with the result, since the other richly albuminous foods produced no result. So that he was led to consider the other abundant constituent of egg-yolk, namely, the fats. Stuckey then fed his rabbits on various animal and vegetable fats, but with absolutely negative result, except in the case of animals which were fed with brain tissue, where slight intimal changes were found. The clue to the truth was given by the work of Anitschkow and Chalutow (2), who, after feeding rabbits on egg-yolk and brain substance, investigated the appearances found in the liver. The cells of the liver parenchyma became laden with droplets of fat, and when these were examined they were found to consist of doubly refracting cholesterin-ester fat. Having found this accumulation of cholesterin in the liver, the probability grew that cholesterin might be the constituent of egg-yolk responsible for the changes in the aortic intima, and so Anitschkow and Chalutow began at once to



feed rabbits on pure cholesterin. By so doing they were able to induce all the intimal changes with great intensity. The microscopic changes produced are briefly these. The change practically affects the intima only, in which fine droplets of doubly refracting fat become laid down. These lie at first extracellularly, and they gradually increase in quantity. Then appear a number of large phagocytic cells, with round nuclei, and much vacuolated protoplasm. These cells are soon found, when examined by the polariscope, to be filled with fine droplets of doubly refractive cholesterin fat. The elastic fibres become separated into a network of fine elastic fibrils, in the meshes of which these large fat-containing cells are seen. Changes of a slight nature are also found in the innermost layer of the media, the muscle fibres becoming separated from one another and somewhat irregularly arranged. These changes approach more closely those found in human arterio-sclerosis than any other arterial lesion so far produced experimentally, and are entirely different from the medial changes which have been brought about by injection of adrenalin, staphylococci, &c. As yet they have only been produced in rabbits, all attempts to reproduce them in dogs, &c., having failed. What their importance is, and what aetiological relationships they may bear to the pathology of human arterial disease, only further work can show.

*The Suprarenal Glands: their Cholesterin Content in Physiological and Pathological Conditions, and their Function in relation to Cholesterin Metabolism.*

Ever since it was recognized from morphological and chemical work that in the body the suprarenals share with the nervous system the distinction of containing the greatest amount of lipoid material in their composition, being especially rich in their cortical part in cholesterin and its ester, many workers have tried to find out the connexion of these glands with the metabolism of fats in general, and cholesterin in particular. It was suggested by French authors at an early period of the work that the increased cholesterin content of the blood-serum, in various conditions we have already referred to, depends directly on an increased suprarenal function. They state in support of this view that in Bright's disease the hypercholesterinaemia is associated with an increase of adrenalin in the blood, and suggest that an increased function of the adrenalin-producing medulla runs parallel with excessive function of the cholesterin-producing cortex. Albrecht and Weltmann (1) came to a similar view from the morphological examination of a large number of suprarenals as to their content in cholesterin-ester in pathological conditions. They found they could divide diseases into two large groups: in one the cortex was rich in doubly refracting cholesterin-ester, in the other group poor in this respect. They explained these differences by alterations in the functional activity of the suprarenals, and would regard these glands as the producers of cholesterin for the organism. Landau (30), from a morphological examination of more than



250 cases, has come to an entirely different conclusion. He concludes that the suprarenals are in no way to be regarded as producers of cholesterin, but that whenever, for reasons which we do not as yet understand, an increased amount of cholesterin is circulating in the body, this simply brings about an increased deposit of cholesterin in the adrenal cortex. In other words, he regards the suprarenal not as a producer of cholesterin, but simply, in its cholesterin content, as an index of the amount of cholesterin circulating in the blood. Landau mentions an ingenious theory of the function of the lipoids of the suprarenal cortex. The suprarenal is a double organ, consisting of a medulla chiefly composed of sympathetic nervous tissue and of the lipid-containing cortex. Might it not be that the lipid-containing cortex is in some way necessary for the sympathetic nervous system (a portion of which it so closely embraces), just as the lipid-containing white matter seems essential to the central nervous system?

Thus there are two theories of the relationships of the suprarenal glands to cholesterin metabolism, the one idea being that they are the factory of cholesterin for the organism, the other that the alterations in their cholesterin content are entirely secondary, depending simply on the amount of cholesterin circulating in the blood at the time. Further work is necessary before we can come definitely to a conclusion. In some recent and as yet unpublished experiments of Aschoff's, in which rabbits were fed with pure cholesterin, the cholesterin content of the suprarenals, which were considerably enlarged, was found by Landau and the author to be enormously increased (see table below). Now we know from the work of Gardner and Ellis, &c., that feeding with cholesterin brings about an increased cholesterin content of the blood, so these experiments favour the view that the changes in the suprarenal cortical cells are a secondary phenomenon to hyper- or hypo-cholesterinaemia in the blood.

Recently, Wacker and Hueck (48) have gone into the question whether the morphological recognition of an increased or decreased cholesterin content of the suprarenals can be confirmed and supported by chemical analysis. They only give results of seven cases where, using the Windaus method, they obtained figures completely bearing out their morphological findings. Landau and the author have, in a research which will shortly be published<sup>1</sup>, gone into this question much more fully, but it will be sufficient here to quote one or two of the results which bring out important points.

The cholesterin content of the suprarenals was in every case estimated by the Windaus method.

<sup>1</sup> In the press. *Ziegler's Beiträge z. path. Anat. u. allg. Path.*, 1914.

*Suprarenal Glands. Amount of Cholesterin per cent.*

Case.	Total Cholesterin %	Free Cholesterin %	Cholesterin-ester %
1. Male, 62 years. Carcinoma of the caecum. Anaemia	0.53	0.06	0.47
2. Male, 52 years. Caseous pneumonia. Aortic aneurysm	0.60	0.19	0.41
3. Male, 46 years. Carcinoma of the oesophagus. Extreme emaciation	1.82	0.85	0.97
4. Female, 36 years. Puerperium. Cholelithiasis. Sudden death — no sepsis	2.92	0.52	2.40
Rabbit, fed on cholesterin over a prolonged period	10.05	1.74	8.31

From the short table it is seen at once that in Cases 1 and 2 the amount of cholesterin present is relatively small. These two cases fall into the category of those in which the cholesterin content of the blood-serum is below the normal, since, as we have previously seen, hypocholesterinaemia is a feature of cancer and of tubercle.

In the puerperal case (4) the amount of cholesterin present is very large, the cholesterin-ester value being especially striking. The result corresponds perfectly with the constant hypercholesterinaemia found in pregnancy.

Case 3 represents fairly well the conditions found in starvation. The carcinomatous stricture was so tight that feeding was impossible, and the patient when sent to hospital was practically dying of starvation. The amount of cholesterin present in the suprarenal cortex is about normal in quantity—certainly not below the normal—which shows that loss of the ordinary neutral fat of the body has no influence on the cholesterin fat, which remains undiminished in the adrenal cortex.

The last figures in the table concern one of the rabbits previously referred to, which was fed on cholesterin. Normally the suprarenal cortex of the rabbit is extremely poor in doubly refracting material, so that the figures found are very noteworthy, nothing approaching them having been obtained in any human suprarenal.

*General Summary.*

Although we are still very far from a complete understanding of the normal functions and metabolic changes of cholesterin in the body, yet much of importance and much that is suggestive has already emerged.

We know much more of the pathological processes with which cholesterin is in some way concerned than of any physiological rôle which it may possess. We know that in a variety of pathological conditions this cholesterin fat is deposited in the organs instead of the usual glycerin or neutral fat. We know,

too, that in pregnancy marked alterations in the metabolism of cholesterol must occur, a fact which is of considerable importance in determining the liability of females to gall-stone formation. In obesity, too, there seems to be an aberrant metabolism of both neutral and cholesterol fats, for the cholesterol changes in the blood-serum are distinct.

As to the normal metabolism of cholesterol in the body, the only view of importance is the hypothesis put forward by Dorée, Ellis, Fraser, Gardner, &c. (17). Much work is necessary here before our difficulties can be cleared up.

The question, too, arises of how far the experimental lesions produced in the aorta of rabbits can be applied to solving the problem of arterial disease in man. It is a fact that as yet the changes have only been produced in rabbits, which are herbivora, all experiments on carnivora, such as dogs, having been abortive. Man being, of course, accustomed to live on a mixed dietary, it must remain at present an open question how far a too richly animal diet might contribute to the development of a condition like arterio-sclerosis. Certainly the old ideas of alcohol, syphilis, &c., as essential causes must be given up, since, for example, Ruffer has shown that in mummies of the eighteenth to the twenty-seventh dynasties (i.e. 3,000 years ago) arterial disease was quite common, although syphilis at that time was unknown. Ruffer also points out that in abstaining Mohammedans arterio-sclerosis is of early and common occurrence.

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While this article has been going through the press, an important contribution to the subject has been made. This is a monograph by A. Grigaut<sup>1</sup>, in which the views of the French school on the origin of cholesterol in the body, and its relations to pathological processes, are clearly set forth. These views have been briefly indicated in the text.

<sup>1</sup> A. Grigaut, *Le Cycle de la Cholestérinémie*, Paris, G. Steinheil, 1913.

## BILATERAL SALIVARY SWELLINGS (MIKULICZ'S DISEASE): A CLINICAL REVIEW

By HUGH THURSFIELD

With Plate 25

### *Introductory.*

IN 1888 and 1892 Mikulicz described a condition of chronic bilateral swelling of the lachrymal and salivary glands, occurring without obvious cause in a previously healthy man of 47 years of age. Since the latter date a large number of cases have been reported under this title, some having a strict similarity to the original type, others varying in detail, but all having at least the characteristic peculiarity of painless bilateral enlargement of the salivary and lachrymal glands, either together or separately. If the term 'Mikulicz's disease' be confined strictly to those patients whose lachrymal and salivary glands are simultaneously or successively affected without involvement of the lymphatic glands or changes in the blood, it is possible to maintain that the affection is in this strict sense a clinical entity. But there are cases on record which illustrate all stages of gradation between this strict type and diseases such as leukaemia or lymphosarcoma. Further, there are cases which at first present the characteristic features of the original type but later develop blood-changes or involvement of the lymphatic system. It is, therefore, now more usual to consider that the affection commonly termed 'Mikulicz's disease' is not a clinical entity but rather a syndrome which may be the result of various causes. A considerable literature has accumulated dealing with cases of the original type and with those which, while retaining the main characteristic feature, yet depart in some respect from the original. The purpose of this paper is to attempt some classification of cases which present as the chief clinical phenomenon bilateral swelling of the various salivary glands in connexion with the mouth. Of the acute bilateral swellings such as occur in mumps, or following specific fevers, e.g. typhoid or pneumonia, or occurring as complications after abdominal operations, I do not propose to speak.

### *Literature.*

The literature dealing with the condition can only be said to date from the publication of Mikulicz's communications in 1888 and 1892, though Haltenhoff (9) quite independently published in 1889 the report of a case in

all respects similar to that which formed the subject of the former communication. In 1897 Kümmel (13) described additional cases under the title of 'Mikulicz's disease', and in 1905 von Brunn (1) and in 1908 Külbs (12) reviewed the previous papers and added fresh cases. Campbell Howard in 1909 wrote an exhaustive account of 'Mikulicz's disease and its allied conditions'; and lastly, in 1910 Igersheimer (10) and Pöllot collected all the known cases of strict Mikulicz's disease, that is, all those in which the lachrymal glands were involved with the salivary glands, and studied them with especial reference to the relationship of the disease to tuberculosis. Since the publication of these last two papers I have found no large collection of cases on record, but there have been isolated cases of considerable interest reported during the years 1910-12. To these I propose to add the record of a patient who in 1913 was under my own observation, and whose illness, unlike the majority of those in which the characteristic features of 'Mikulicz's disease' are prominent, ran a rapidly fatal course.

*Case (Figs. I and II).* A man, aged 30 years, of Jewish birth, a tailor's cutter by trade, enjoyed good health till July, 1913. He then had an attack of tonsillitis, was in bed some days, but at the end of a fortnight had recovered and resumed his work. In the middle of August he was told by his friends that he had 'mumps', since both sides of his face were swollen; he himself had no pain and was unconscious of any swelling until it was pointed out to him. For several days after they were first noticed the swellings increased in size, and then became stationary; a few days later he began to feel very tired at his work and to suffer from attacks of giddiness, shortness of breath, and palpitation. From August 18 to August 20 he could speak only in a hoarse whisper, but then recovered the full use of his voice. At no time had he any pain or tenderness in the swellings, but had been conscious of a dryness of the mouth and tongue. There was no family or previous history of disease.

I saw him first on September 6. He was a well-built man, somewhat thin with a sallow complexion, and pronouncedly anaemic. His voice was slightly husky but strong. His eyes were prominent, but there was no trace of enlargement of the lachrymal glands; the pupils reacted to light and accommodation; the ocular movements were perfect; and there was no conjunctivitis or keratitis. He complained of some discomfort in the ears, and was slightly deaf, a condition which became markedly worse during the following week. There did not appear to be any disease of the middle ear. The parotid glands were uniformly enlarged, firm, smooth, without tenderness; the socia parotidis on either side formed a distinct tumour. The enlargement was moderate in degree. The sub-maxillary glands on both sides were also enlarged; they also were painless, not tender to pressure, and the skin over them neither reddened nor oedematous. They formed a distinct collar round the front of his neck. The sublingual glands were not enlarged and there were no tumours of the hard palate, like those observed by Mikulicz in his original patient. The lymphatic glands in both posterior triangles of the neck were moderately enlarged and also those in front of the sternomastoid muscles. The axillary glands were enlarged on both sides, the largest individual gland being about the size of a walnut. They were soft and easily movable beneath the skin. The inguinal glands were palpable but quite small. The tonsils were not large; the teeth were ill-kept, and there was a moderate degree of pyorrhoea alveolaris in connexion with the lower incisors. The liver and spleen were not felt to be enlarged. Nothing abnormal was detected in the heart or lungs or abdomen. Ophthalmoscopic examination



showed a normal fundus. The knee-jerks were normally active and the plantar reflexes flexor in character. The urine contained neither albumin nor sugar nor pus cells. A blood-count made on September 6 read as follows:—

Red blood corpuscles . . . . .	2,440,000 per c.mm.
White blood corpuscles . . . . .	2,000 " "
Haemoglobin . . . . .	52 per cent.
Colour index . . . . .	0.9.

Of the white cells 340 per c.mm. were polymorphonuclear: 1280 were lymphocytes; 360 were large mononuclear and 20 were eosinophil cells. No nucleated erythrocytes were seen.

I may record here the results of later blood examinations.

	R. B. C.	W. B. C.	Hgb.	C. I.	Polym.	Lymph.	L. M.	Eos.
11. ix. 13		1,600			480	1,120		
20. ix. 13	3,620,000	1,800	64 %	0.7				
27. ix. 13		700			112	574	14	
1. x. 13	230,000	400			216	132	44	8

No nucleated erythrocytes were found at any examination. A blood-culture made on 25. ix. 13 was sterile.

The patient had at first no fever, but at the end of the first week in the hospital began to have irregular fever, which at the end of the second week had become considerable, 103° F. In the third week up till death the temperature did not sink below 102° F.

On September 27 it was noticed that there was a marked diminution in the size of the parotid and submaxillary swellings, and in the few days preceding death there was no longer any visible or palpable enlargement. The same diminution was observed in the cervical and axillary glands. The spleen, at first impalpable, in the second week extended an inch below the costal margin, but then diminished, and in the third week could no longer be felt. The total duration of the illness from the date of the first observation by the patient of the parotid swelling was thirty-four days. In the belief that the disease was due to an infection, an attempt was made to isolate an organism from the parotid glands. To secure the secretion of the glands in some quantity an injection of  $\frac{1}{8}$  gr. of pilocarpin nitrate was given beneath the skin and the saliva collected in sterile pipettes as it flowed from the duct. A streptococcus isolated by this means was used to prepare a vaccine, which, however, produced no effect. Later, anti-streptococcic serum was employed, but without appreciable influence on the course of the disease.

Permission for an autopsy was refused.

It is obvious that this case differs in almost every respect from the original type of 'Mikulicz's disease'; there was no involvement of the lachrymal glands; and, on the other hand, the lymphatic apparatus, glands, and spleen certainly shared in the affection; and there was a profound and peculiar change in the blood-picture. The sole point of resemblance was the prominence of the bilateral salivary swellings. Mikulicz himself, however, recognized that there were variations in the clinical phenomena, and other writers have emphasized the fact; in cases which otherwise correspond to the type the lachrymal glands may escape, e.g. Ranzi's (20) case; or a patient who at first exhibits no alteration in the lymphatic apparatus or the blood-picture may later develop

profound changes in both directions, e.g. Marcuse's case; so that the clinical connotation of 'Mikulicz's disease' has become indefinite.

In the literature I am acquainted with but one case which is in any degree parallel with that recorded above, that of von Brunn (1). Halpern's (8) case of a male, aged 26, who with bilateral submaxillary swellings and enlargement of the axillary and inguinal glands exhibited an aplastic anaemia, at first sight appears to be of the same type; but the presence of a large mediastinal tumour raises the suspicion that the case ought really to be grouped with the lymphosarcomata. Halpern named it aleukaemic lymphomatosis.

*Case (von Brunn).* A girl, aged  $4\frac{1}{2}$  years, of good health previously, suddenly developed, without ascertainable cause, symmetrical swellings of the lachrymal, parotid, submaxillary, and sublingual glands. The spleen was not palpable, but there was an enlargement of the lymphatic glands in the neck, in both axillae, and both inguinal regions; the epitrochlear glands on both sides were also swollen. A blood-count showed:—

Red blood corpuscles . . . . .	2,750,000 per c.mm.
White blood corpuscles . . . . .	2,610 " "
Haemoglobin . . . . .	35 per cent.
Colour index . . . . .	0.6.

Differential count of the white corpuscles:—

Polymorphonuclear cells . . . . .	775 per c.mm.
Lymphocytes . . . . .	1,474 " "
Large lymphocytes . . . . .	216 " "
Large mononuclear cells . . . . .	44 " "
Transitional cells . . . . .	95 " "

There were no nucleated erythrocytes, no eosinophils, and no myelocytes. Later counts showed the same characteristic features, and von Brunn concludes that the blood examination showed evidence of an aplasia of the bone marrow. In spite of treatment with X-rays, which caused a diminution of the swellings, the general condition became worse, and there appeared infiltrations of the skin over the skull, and thickenings of the periosteum of the long bones. The child died six months from the onset of the swellings. There was no autopsy, but the lachrymal glands had been removed during life, and were available for histological examination. The microscopic sections showed a massive infiltration with lymphocytes. von Brunn prefers a purely descriptive title for this case: severe anaemia with lymphatic pseudo-leukaemia and aplasia of the bone marrow.

The points of resemblance between this case of von Brunn's and my own are obvious: the sudden onset, the bilateral swellings of the salivary glands, the unusual character of the blood-picture, which is almost identical in the two cases, the extensive involvement of the lymphatic apparatus, and the fatal termination. In von Brunn's patient there was also the striking infiltrations of the skin, and the periosteal affection, which had no counterpart in mine. I think that there can be no doubt that the two cases are examples of the same affection.

But of what affection? It is clear that both in the onset, in the character of the blood-changes, and in the fatal termination they differ markedly, both

from 'Mikulicz's disease' of the original type and from nearly all those recorded since under this title. If, however, we leave out of consideration for the moment what I may call 'the Mikulicz symptoms', that is, the symmetrical swellings of the salivary glands, and devote attention to the blood-changes and the general course of the disease, I believe that the two cases fall easily into the group known as that of aleukaemic leukaemia. Of this group I have seen two or three cases in which the examination of the tissues after death, especially of the bone marrow, revealed lesions which were identical with those found in cases of acute lymphocytic leukaemia; and in these cases the blood-changes during life were strictly similar to those under consideration, i.e. a marked diminution in the number of white corpuscles, especially of the polymorphonuclear cells, and the absence of nucleated erythrocytes in spite of the severe anaemia. Further, the massive infiltration with lymphocytes found in the sections of the lachrymal glands of von Brunn's patient reminds one forcibly of the similar lesions found in the tissues of patients dead of leukaemia. The skin infiltrations mentioned by von Brunn are not very common in leukaemia, but occur in a sufficiently large proportion to be now well recognized as a symptom of the disease. The swelling of the lymphatic glands of various regions, the involvement of the spleen in my case, and the course of the disease, all coincide with the clinical type of acute leukaemia.

To return to the 'Mikulicz symptoms', Can it be shown that cases of undoubted leukaemia exhibit this phenomenon? There are at least three well-authenticated cases, those of Dunn (2), Stock (23), and Senator (22), in which the fatal illness started with swelling of the lachrymal and salivary glands, or of the salivary glands alone, and presented all the characteristic features of leukaemia. (See note at end.)

In spite, then, of the absence of post-mortem confirmation, I think that my own case and that of von Brunn may confidently be classified as examples of atypical (aleukaemic) leukaemia, exhibiting the rare phenomenon of bilateral enlargement of the parotid and submaxillary glands, and in von Brunn's case of the lachrymal glands also. Their relationship to 'Mikulicz's disease' proper is considered later.

#### *Review of the Literature.*

This relationship will be best studied by reviewing briefly the various types of cases in which the 'Mikulicz symptom-complex' has been a prominent feature.

von Brunn (1), writing in 1905, offered a somewhat elaborate classification:—

##### I. Cases without alterations in the blood.

##### A. Without swelling of the spleen or lymphatic glands.

- (a) Symmetrical swelling of the lachrymal and salivary glands.
- (b) Symmetrical swelling of the lachrymal glands alone.
- (c) Symmetrical swelling of the salivary glands alone.

B. With swelling of the spleen or lymphatic glands.

(a) Symmetrical swelling of the lachrymal and salivary glands.

(b) The same, with infiltrations of the skin.

II. Cases with alterations in the blood.

A. Severe anaemia with lymphatic pseudo-leukaemia and aplasia of the bone marrow.

B. Leukaemia.

In this classification the case which I have recorded above and von Brunn's similar case would be placed under II, A; if, however, the interpretation which I have suggested were accepted, Class II would consist only of cases of leukaemia, and von Brunn's II, A would disappear.

In von Brunn's classification one of his own cases, Mikulicz's original case, and eight others fall into I, A (a); into I, A (b) fall the cases of Power, Abadie, Pick, and others; and into I, A (c) four of the cases recorded by Kümmel. The cases reported by Osler, Hirsch, Zirm, and others belong to I, B (a); and a single case, that of Haeckel (7), to I, B (b). From Haeckel's account, however, it seems possible that his case was in reality another example of aleukaemic leukaemia; the blood is stated to have been normal, but was apparently examined upon one occasion only, and no details are given. The skin-infiltrations, the great enlargement of the spleen, the fever, the course of the disease, and the histology of the tissues post mortem, are all in accordance with the phenomena of leukaemia.

Campbell Howard's exhaustive paper adopts a simpler mode of classification into three main groups: (i) Mikulicz's disease proper; (ii) pseudo-leukaemia; (iii) leukaemia. In the first group he places those cases in which there was swelling of the lachrymal and salivary glands, either together or separately, without alteration in the blood, or enlargement of the lymphatic glands, and running a benign course. Of such cases he has collected fifty-five up to the year 1909, showing all stages of gradation from enlargement of one gland or pair of glands only to complete involvement of all the glands. The swellings are smooth, firm, and painless, and do not adhere to the adjacent tissue; the lachrymal glands are, as a rule, involved first; the salivary later. Such a condition, apart from the disfigurement, is of little moment; at most there is diminution of the saliva, leading to xerostomia, and some slight difficulty in mastication, owing to the swelling of the parotid glands. In some few cases there is iritis or irido-cyclitis, a point to be noted later. Operation upon the lachrymal tumours is usually completely successful, since there is no tendency to recurrence.

To the second group Howard has attached the name pseudo-leukaemia; an unfortunate choice, since there are few terms in medicine which have had to bear so great a variety of meanings. Howard's meaning is that to the glandular swellings of the first group is added involvement of the lymphatic glands and often of the spleen. The blood shows no material alteration from the normal standard, save that the haemoglobin is often below par; especially there is no

increase in the number of the white corpuscles. In this group are included cases in which the disease terminated fatally, and Howard himself observes that more careful examination of the blood might have removed some of the cases to the third group, that of leukaemia. In this second group he has placed twenty cases, including von Brunn's quoted earlier in this paper, Haeckel's case already mentioned, and a case reported by Marcuse which terminated fatally with extensive involvement of the lymphatic tissues, especially of the mediastinal glands. Of von Brunn's case he says, 'A true leukaemic blood-picture might have developed had not death supervened.'

Of true leukaemic cases Howard accepts six, rejecting others on the score that neither lachrymal nor salivary glands were enlarged, but only the orbital tissues invaded by the cellular infiltration, a condition often observed in leukaemia.

Since the publication of Howard's paper some interesting isolated cases have been recorded. Of Mikulicz's disease proper Elliot (3) recorded a typical example in a Hindu woman, aged 47, who, following an attack of conjunctivitis, had suffered from bilateral painless swellings of the lachrymal, parotid, and submaxillary glands. There was no enlargement of the spleen or lymphatic glands, and the blood-picture was normal. Operation on the lachrymal glands was successful, and was followed by diminution in the parotid and submaxillary swellings. Ingram, who examined the tissues microscopically, came to the conclusion that the best term to apply to the cellular infiltration of the glands was 'lymphomatous'.

Fritzsche's (4) case had no lachrymal swelling, but appears from an inadequate account to have been an example of the strict type.

Battle's (24) case, reported as 'Mikulicz's disease', was thought to be an instance of leukaemia, though no blood examination was made.

Krailsheimer (11) reported a case with the characteristic lachrymal and salivary swellings, complicated by an irido-cyclitis of both eyes. The submaxillary glands on removal proved to be the seat of chronic interstitial inflammation, and numerous tubercle bacilli were demonstrated in the stroma and acini of the gland. Napp (17) had previously reported a case in which tuberculous infection was undoubtedly the cause, tubercles being present in the tissues of the lachrymal gland and the bacilli being demonstrated. Plitt's (18) is the only other case I have found in which the positive proof of the demonstration of the bacilli is available. The patient, of whom a photograph (Fig. 3) is given, was a boy, aged 17, who with a double irido-cyclitis had bilateral parotid swellings; the lachrymal and submaxillary glands were not enlarged. He was believed to be the subject of tuberculous infection and was treated with injections of tuberculin. Improvement followed, and after a time the patient ceased to attend and has not been since seen.

There are a number of other cases in which a suspicion of tuberculous infection has been entertained, and after an exhaustive review of the ophthalmological literature Igersheimer and Pöllot (10) conclude that though tuberculosis



does occasionally give rise to the symptom-complex of Mikulicz, the occurrence is exceptional and the great majority of such cases has nothing to do with tuberculosis.

Syphilis has, of course, been suspected to be a cause of bilateral salivary swelling, but so far as I can ascertain, the positive proof of the demonstration of the *Treponema pallidum* has not yet been recorded. On clinical and therapeutic grounds the connexion is probable. Two recent cases in which a periodic bilateral parotid swelling followed infection with syphilis are recorded by Lange (14) and Lüders (16); and Gutmann (6) reported that of a man of 27 years of age in whom the 'Mikulicz' symptoms appeared three years after the primary affection and were completely removed in two months by the use of large doses of potassium iodide. Jakobäus (26) has also reported two cases in which there was a definite history of syphilitic infection; one of a man, aged 49, who had both lachrymal, both parotid, and both submaxillary glands enlarged, with swelling of the axillary and inguinal glands, and of the liver and spleen. The Wassermann reaction was positive. Anti-syphilitic remedies failed to benefit the condition, and the patient died of cachexia. Microscopically there was lymphocytic infiltration in all the organs examined. Jakobäus considered that the condition was a 'granulomatosis'. The blood-count showed consistently a high red corpuscle count, ample haemoglobin, and a normal number of white cells; the lymphocytes were somewhat increased at the expense of the polymorphonuclear cells. The other syphilitic case was that of a girl of 18 years of age, in whom swelling of one parotid was followed a year later by enlargement of the other. There was a typical syphilitic roseola and the Wassermann reaction was positive, but anti-syphilitic therapy produced no diminution of the glandular swellings, which eventually disappeared with the applications of X-rays.

Of the other two cases reported by Jakobäus, one was typical 'Mikulicz's disease' in a woman, aged 62, much benefited by X-rays; the other a most unusual affection in a child, aged  $4\frac{1}{2}$  years. This child had a tumour of the inguinal glands, followed several months later by a spontaneous fracture of the tibia. Later both parotids and both submaxillaries were enlarged and the cervical and axillary glands and spleen swollen. There were also periosteal thickenings and infiltrations in the skin of the skull; the latter are said to have had a greenish tinge. Jakobäus speaks of the disease as an example of 'chlorolymphomatosis'. I have been unable to consult the original paper of Jakobäus, and the abstract on which I have had to rely, though lengthy, does not enter into full details; but since the blood-count is said to have been normal, I venture to think that it is rather to be classed among the examples of lymphosarcomata.

Of other generalized diseases in which the symptoms may appear, gout is the only one in which the evidence as to the connexion between the disease and the symptoms seems to be in any way satisfactory. Some years ago Debout d'Estrées described the phenomenon, and more recently Deglos (25) has pub-



lished an interesting example in a lady, aged 64. The swelling in these cases, however, appears to be usually acute and transitory.

Another group of cases, exhibiting bilateral swelling of one or more pairs of salivary glands, has an additional characteristic feature which serves to mark it off sharply—the intermittent recurrence of the swellings. This recurrent parotitis has been recognized for some years, and is distinguished by the sudden onset of the swelling, usually soon after taking food, by the absence or marked diminution of the saliva, by the occasional febrile attacks with the onset, and by the complete subsidence of the swelling in the intervals. Of such cases Greig (5) has reported a typical example in a lady, aged 35, who in the course of a few years had six separate attacks. The cause of this affection is believed to be an acute inflammatory swelling of the lining of the parotid or submaxillary ducts and a subsequent extension of the inflammatory exudation into the substance of the glands. The duct is blocked by a fibrinous plug which can be felt and sometimes seen in the mouth. The name of 'sialodochitis fibrinosa' has been proposed for this affection, which is almost certainly of bacterial origin, though observations as to the nature of the invading organism have been seldom made. Generally a streptococcus of feeble virulence has been isolated. Battle's case, reported in 1895, seems to have belonged to this group.

Quincke's (19) remarkable case of a man, aged 45, whose parotid glands had been symmetrically enlarged since birth, and in whose family the father, two uncles, five brothers, and two sisters exhibited the same peculiarity, appears to point to the existence of a congenital family form of the disease. A similar case was reported by Leri (15) in an Algerian, aged 27, in whom symmetrical parotid, submaxillary, and sublingual swellings had existed since birth. The patient alleged, but Leri was unable to confirm the statement by personal observation, that his father, two of three brothers, and two of four sisters were similarly affected, besides several uncles and aunts. Leri refers to a paper by Fontoynt (28), describing a similar hereditary and family affection in Madagascar, where it is locally known as 'le mangy'. (See note at end.)

#### *Summary.*

Clinically, therefore, it is possible to recognize at least eight groups of cases in which bilateral swellings of the salivary glands, either with or without an accompanying enlargement of the lymphatic glands, form the most characteristic symptom:—

1. A congenital, hereditary, or family affection.
2. 'Mikulicz's disease' proper.
3. 'Mikulicz's disease' with involvement of the lymphatic apparatus.
4. Leukaemia.

5. Tuberculosis.
6. Syphilis.
7. Gout.
8. Sialodochitis fibrinosa; intermittent or periodic salivary swelling.

In addition there are from time to time met with cases which do not appear to belong to any of these groups; and to two of these reported recently I must here make reference. Schoenbrun (21) in 1910 described the case of a man, aged 44, who after an attack of tonsillitis and pyorrhoea alveolaris felt a stiffness and discomfort in the tongue and cheeks and a progressive weakness in the muscles of the face and neck. The tissues of the chin and submaxillary regions became thickened; the tongue increased rapidly in size; and the muscles of the shoulder-girdle became hypertrophied. The lachrymal glands and the lymphatic tissues were not affected. Wassermann's reaction was negative; the blood examination revealed nothing abnormal, and a microscopical examination of a portion of the submaxillary gland gave no information. Schoenbrun discussed the possible diagnoses and came to the conclusion that the case was one of chronic toxæmia. It is à propos to recall the statement that sufferers from chronic lead poisoning occasionally exhibit a chronic enlargement of the salivary glands.

Plate and Lewandowsky (27) report a case which is, I believe, unique. A healthy boy, aged 12, on June 11, 1911, had some reddening of the conjunctivæ, followed on June 13 by a swelling of both parotid glands. This was diagnosed as mumps, although the boy had some years previously suffered from that affection. A few days later painless swelling of the sublingual and submaxillary glands occurred, and on examination the axillary, cervical, and inguinal lymphatic glands were found moderately enlarged and the spleen two fingers'-breadths below the costal margin. The boy looked pale, but had 5,000,000 red corpuscles per c.mm. and no increase of the white cells. A blood-culture made at the time the temperature was raised to 100·8° F. was sterile. Shortly there appeared on the legs an eruption, having all the characters of an erythema nodosum. This eruption remained and went through the usual colour changes, gradually fading; fresh infiltrations appeared from time to time, limited to the legs below the knee, save that on one occasion a few spots were seen on the buttocks. By July 19 the boy was sufficiently recovered to go to the seaside. On his return in August there was still a hard resistance to palpation in the parotid glands, and the spleen was still palpable; the exanthem was recurring at intervals. In December, 1911, there was a fresh swelling of the lymphatic glands and spleen, but this time none of the salivary glands. In January the sublingual glands were slightly enlarged. A piece of skin from the leg was excised for microscopic examination, and showed chronic inflammatory infiltration, fibroblasts predominating. From this time the patient improved steadily, and at the end of seven months recovery was complete. The reporters of this case consider the possible explanations and conclude that it was an example of chronic infection with an unknown organism. The Wassermann and von Pirquet reactions were alike negative.

*Pathology.*

When we review the various types of disease in which symmetrical swelling of the salivary glands is the prominent feature, and consider their relationship to each other, it is clear that there is no one underlying cause; the same clinical characteristics may be produced by a variety of infections. That the underlying cause is an infection was the view supported by Mikulicz himself. The association with inflammatory affections of the pharynx, conjunctivae, and mouth; the characteristic histology of all cases of 'Mikulicz's disease' proper, consistent with a chronic irritation of the tissues; and the general course of the disease all point to the correctness of this hypothesis, but there is, as yet, no indication of the nature of the infecting organism, except in the tuberculous, syphilitic, and streptococcic groups. It would appear quite clear that the disease originally described by Mikulicz is, if not the same, at least very closely allied to the affection which involves the lymphatic tissues, and that in turn closely related to the true leukaemias. Marcuse's case, which at first was diagnosed as 'Mikulicz's disease', later developed blood-changes and terminated fatally; and Stock's case, at first without blood-changes, terminated as a frank leukaemia. The histology, also, is very similar throughout; the round-cell infiltration of the tissues in the most benign cases strongly resembles that found in the most acute and rapidly fatal cases of leukaemia. A curious feature of the disease noted in many cases is the tendency of the swellings to diminish and even to disappear in the presence of an acute bacterial invasion, e.g. erysipelas or pneumonia. What may be the explanation of this phenomenon is quite unknown, but it is a well-recognized feature in leukaemia, in which disease the glands and the spleen often diminish remarkably in the course of a few days, to grow again as soon as the acute complication is past.

The only other possible hypothesis is that the disease is a new growth; and this does not fit the facts nearly so well. In truth it agrees only with the phenomena of the original type, in which it might be conceded as possible that the swellings are a benign tumour-formation. Further speculation in the absence of new facts is useless.

*Prognosis and Treatment.*

The probabilities as to prognosis have already been sufficiently indicated. When there is no involvement of the lymphatic glands or spleen and no alteration in the blood, the disabilities of the affection seem to be confined to the disfigurement, and to a certain degree of occasional discomfort, from both of which the lapse of time, one to five years as a rule, releases the patient. When the lymphatic glands or the spleen are enlarged the outlook is more uncertain; of Howard's twenty 'pseudo-leukaemic' cases six died, and of the definitely leukaemic cases Stock's patient alone survived more than six months.

The tuberculous, syphilitic, and infective cases will, of course, be treated by appropriate methods; though it is probable that in all such cases the administration of arsenic will be found beneficial. For the other cases, at any rate, arsenic would seem to be of greatest value, whether administered in the form of a pill by injection, or as Fowler's solution. I have not found any case recorded in which salvarsan was administered, but it would appear to be particularly well adapted for use in a disease which yields, if at all, only to massive doses. In some few cases potassium iodide has been used with benefit, even where there has been no suspicion of syphilis.

Operative removal of the enlarged lachrymal glands in some instances favourably influences the size of the salivary swellings, as in Elliot's case and some others, but this is not invariable. The submaxillary tumours have also been removed, but I have not found any case where the parotid swellings have been attacked in this way. After removal of any of these tumours there is no tendency to recurrence.

On the whole, the treatment which appears to promise the best results is to remove carefully any possible source of chronic infection, e.g. decayed teeth; to seek to establish the general health; to give arsenic in the largest doses which can be tolerated, and to treat the actual swelling with X-ray applications. In Ranzi's case the swellings disappeared twice with X-ray treatment, and after the second course did not return. Success is certain to be slowly won, and in spite of all endeavours some patients will remain permanently disfigured by this obscure complaint.

#### NOTES.

PAGE 241. A fourth case of undoubted leukaemia has come to my notice since the above was written. The patient, a child of 2 years of age, suffered from acute lymphocytic leukaemia, in the course of which parotid and submaxillary swellings appeared; the lachrymal and sublingual glands were not involved. The case was, in respect of the blood-count, intermediary between mine and von Brunn's and the more typical leukaemias; the highest leucocyte-count being only 14,700 per c.mm. and falling to 6,700 before death. The case is fully reported by Tileston.

PAGE 245. It is frequent on the high plateaux, rare on the coasts; limited to a few localities, but in these affecting many individuals. The lachrymal glands are not affected; but all the salivary glands, either separately or simultaneously, are swollen, firm, painless, and usually smooth, though occasionally nodular. It is not congenital, but usually appears early in childhood, and remains through life.

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#### DESCRIPTION OF PLATE.

FIGS. 1 and 2. Photographs of the salivary swellings in author's case.

FIG. 3. Photograph of a boy of 17 years of age, the subject of a bilateral parotid swelling with irido-cyclitis, believed to be of tuberculous origin. [This photograph I owe to the kindness of my colleague, Mr. Gordon Watson.]





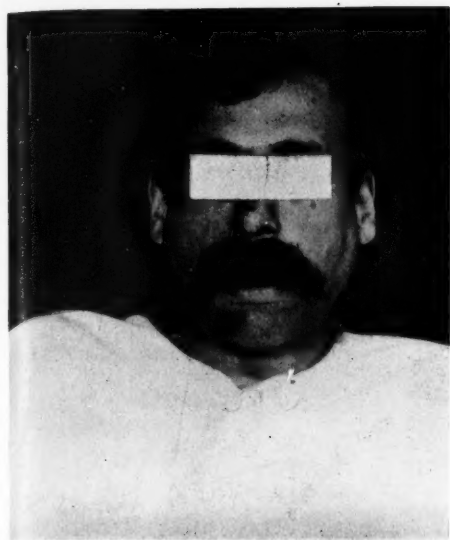


FIG. 1



FIG. 2

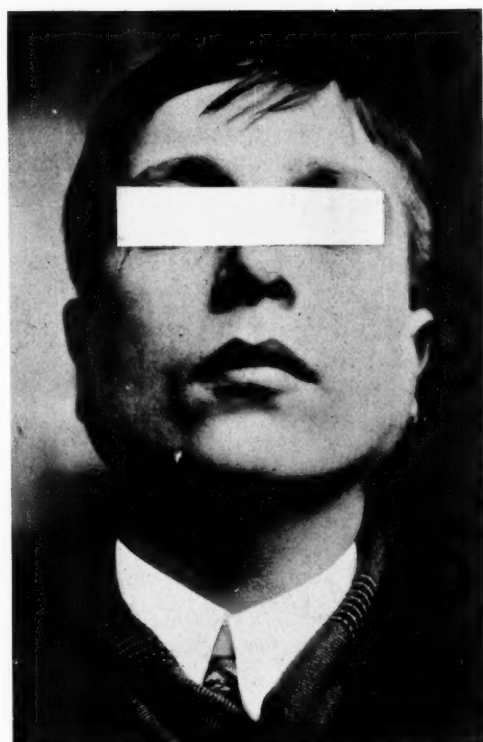


FIG. 3



# ON THE PROGNOSIS OF ACUTE ARTICULAR RHEUMATISM, WITH SPECIAL REFERENCE TO THE CARDIAC MANI- FESTATIONS

By CHARLES G. KEMP

(From the Radcliffe Infirmary, Oxford)

RHEUMATISM, acute and subacute, is, in its effects, one of the most serious and at the same time one of the commonest diseases met with in hospital medical practice. During the year 1911 the number of such cases received into the Radcliffe Infirmary and County Hospital, Oxford, with sixty-five medical beds, was twenty. This gives an incidence of 3 per cent. of all medical cases admitted, a figure considerably less than half that given for Oxford as the average of eleven years in Allbutt and Rolleston's *System of Medicine*, that is 7.64 (1). The number of patients with chorea admitted during the same period was sixteen, eleven of which had heart disease, old or recent.

The cases of heart disease, grouped under the terms of morbus cordis and pericarditis, numbered thirty, and of this number fifteen (or 50 per cent.) gave a definite history of rheumatism. In five cases there was a history of chorea; in eight, a history of sore throat; and in four, of growing pains or stiff neck, some of the cases having a history of one or more of these conditions (all of which are taken as evidence of specific rheumatic infection), in addition to that of acute articular rheumatism. In two cases only was there a history of scarlet fever as a possible cause of the heart disease.

From these figures it will be seen that about half of the heart cases among the hospital class, occurring in Oxfordshire and the adjoining part of the Thames valley, are of rheumatic origin.

As the prognosis in acute rheumatism depends almost entirely on the condition in which the heart is left after the acute attack, three questions are suggested:—

1. How many patients run the course of their illness to complete convalescence without showing clinical signs of cardiac involvement?
2. How many, having shown such signs during the acute stage of the illness, go on, either during convalescence or at a later date, to complete cardiac recovery?
3. Upon what factors does this recovery, if it occurs, depend?

It is with these questions in mind that I have endeavoured to work through

the cases of acute and subacute rheumatism which have been treated in the Radcliffe Infirmary between the years 1903 and 1909, both inclusive; and I have to thank the Honorary Medical Staff of the hospital for their kindness in allowing me to use the case-records.

All cases of chorea have been omitted, chiefly on account of the large number of cases which would have to be dealt with and the difficulties involved in following up so large a number in a scattered country district.

The cases of acute and subacute rheumatism treated during the year 1911, during most of which time the writer was House Physician, have also been collected and analysed, and it is hoped that some comparison may be drawn between the immediate and remote effects of rheumatism on the heart—the remote effects being worked out on cases which have left hospital from two up to nine years ago, from the time of writing.

#### *Definitions.*

In the first place, a word of explanation is necessary as to what is meant by the terms acute and subacute rheumatism.

(a) By *acute rheumatism* is meant a specific infection, characterized by multiple arthritis, the synovial membrane being affected, with effusion of fluid, and fever, both yielding to salicylate medication.

(b) By *subacute rheumatism* is meant a similar condition, but with less intense arthritis, although in some instances of longer duration, and less fever; in fact, a condition in which all symptoms are less pronounced but more prolonged. This form of the disease also yields wholly or in great part to treatment with salicylates.

There is only one exception to this rule in the series of cases here reported, namely, a girl, aged 16, with acute articular rheumatism, in whom salicylate of soda produced temporary delusional insanity. She was therefore treated with quinine and alkalies, a good recovery resulting. All other cases of arthritis which have not yielded to salicylates have been excluded from the series.

#### *The Criteria of Rheumatic Cardiac Affections.*

No one in daily attendance on cases of rheumatic fever can fail to be struck with the way in which the condition of the heart alters from day to day. On many occasions one has seen such cases admitted to hospital early in the disease with the heart sound and normal, both in size and on auscultation. The patient quickly responds to salicylate of soda, the temperature falls, and the patient is comfortable. Then the heart begins to show signs of a certain amount of dilatation and a blurring and lengthening of the mitral first sound occurs, later developing into a definite soft systolic murmur, which may or may not be conducted into the axilla. This may persist for days or even weeks, and then the dilatation subsides and the mitral murmur disappears, the first sound becoming clear and valvular once more. Other cases occur in which the

murmur remains after the patient leaves hospital, but which is found to have disappeared when the heart is examined months later. This phenomenon occurs with comparative frequency, and one must attempt to explain its occurrence.

Three hypotheses are advanced:—

1. That the rheumatic organisms circulating in the blood set up an endocarditis on the thin valve cusps, resulting in the formation of vegetations and roughening of the thin edge of the valve, so setting up a vibration in the circulating blood-stream which is heard as a murmur. This explanation is highly improbable for two reasons:

(a) The organisms which give rise to the endocarditis are hardly likely to pick out the edges of the valves as a place to settle, seeing that at these places the blood-stream is passing with its maximum rapidity. They would be far more likely to select a portion of the endocardium where the blood-current is more stagnant, such as the auricular appendices; but this does not occur typically.

That the organisms are actually found on the surface of the valves has been proved experimentally in animals by Poynton; but, as will be pointed out later in the pathological section, Carey Coombs has shown that the organisms get to the surface from the deeper part of the valve, the area of inflammation 'pointing' towards the endocardium. The result of this is the formation of superficial ulcers on the valve surface with deposit of fibrin from the circulating blood and the formation of the typical vegetation. But the point is that the organisms are *primarily* carried to the valve by the coronary circulation, though more are probably added from the main circulation with the deposition of fibrin.

(b) Examined post mortem, it is inconceivable that the row of minute jelly-like vegetations seen in a case of recent endocarditis could set up vibrations sufficient to cause the murmur heard during life.

2. That there is, in the milder cases, a local hyperaemia set up in and around the infected valve in a case of recent infection, producing temporary incompetence by the weakening of the valve structures. If the local infection is not severe this may not lead to enough scarring to cause any permanent valvular defect.

3. That the endocardium escapes, at any rate to any serious extent, and the rheumatic poison acts on the heart muscle itself, causing weakening and consequent stretching of the chambers of the heart and of the ring of insertion of the valves, especially the mitral and tricuspid; the semilunar valves, for anatomical reasons, not being affected in the same way. This will cause a relative incompetence of the valves, not from the fact that they are themselves diseased, but because for the time being their base of insertion is stretched, and the cusps are no longer large enough to close the space, which under normal circumstances they can do with ease. This seems the most reasonable explanation, and is, moreover, upheld by post-mortem examination, the orifice of the mitral valve being found in a number of cases to be larger than normal, without any disease of the valve segments. It is reasonable to suppose that (2) and (3) may exist together.

Again, diastolic murmurs are heard occasionally at the mitral area, in early rheumatic carditis, especially in children. These murmurs are mid-diastolic in time, and are soft, unlike the crescendo presystolic murmur produced by a thickened and cicatrized mitral valve. Carey Coombs offers an interesting explanation of these murmurs. He points out that such murmurs are always associated with cardiac dilatation, especially of the left ventricle. The left ventricle becomes increased in capacity, out of proportion to the amount of stretching of the mitral ring, and he regards the murmur as being due to vibrations set up in the blood which is sucked into the ventricle during ventricular diastole, rather than forced into it during auricular systole, the mitral orifice being relatively narrowed, and a 'fluid vein' being thereby produced. That there is in reality no actual narrowing of the mitral orifice, but rather a stretching, he has shown by post-mortem examination on cases in which this murmur was heard, the cases having been diagnosed as mitral stenosis. This explanation accounts for the rapid disappearance of the murmur with rest, and the resulting decrease in size of the ventricle.

This is undoubtedly one of the ways in which organic valvular disease is diagnosed without sufficient justification. In the series of cases analysed in this essay there is no example of this diastolic murmur, but I hope to show that cases which have been diagnosed in hospital as mitral regurgitation are in reality due to myocarditis, and that it is quite unnecessary to blame the valves for the physical signs produced.

#### *The Pathological Basis of Prognosis.*

In order to justify, and I hope to prove, the statements which have been made so far, it is necessary to review shortly the more recent pathological researches on the subject of rheumatic heart disease.

Brooks (2) gives an interesting summary of the pathological changes in the heart in 187 cases examined post mortem. He maintains that the prognosis of endocarditis rests mainly on the condition of the heart muscle and on the character and degree of the associated muscle change, rather than on the extent of the valvular lesions. He points out that physiological incompetence of the valves is often not to be demonstrated post mortem, being due (as has already been mentioned) to muscular and not to valvular defects.

Brooks mentions a variety of ways in which the heart muscle becomes involved in endocarditis, the most important being the following:—

1. It becomes diseased as a result of the process or condition under which the endocarditis develops; e.g. acute parenchymatous degeneration of the myocardium in rheumatic fever arises from the same cause, bacterial or otherwise, which produces the inflammatory condition of the valve surfaces.

2. A diseased valve vegetation may become loose, or bacteria circulating in the blood may cause embolism of a coronary arteriole, the result being infarction of a portion of the heart muscle, followed by necrosis in the area supplied by the



blocked arteriole, and then cardiac rupture; or, if fibrosis occurs in the diseased area, a cicatricial scar or aneurysm results.

3. The involvement of the heart muscle may begin in the papillary muscles which have first been weakened by the over-stretching which follows valve incompetence, and consequent stretching of valve rings. From these foci more or less general fibrosis extends. Invasion of the papillary muscles is common in chronic endocarditis and is responsible for valve incompetence.

Brooks has also shown from examination of hearts post mortem that by far the commonest and most important changes are those of a degenerative nature, true inflammatory changes being rare. He finds that mitral endocarditis is accompanied by less myocardial change than any other valvular lesion, whereas lesions of the aortic valve show most change.

Carey Coombs (3) has done a considerable amount of work on the morbid histology of rheumatic hearts. He has examined heart muscle which macroscopically appeared normal, and has in no case failed to find definite evidence of myocarditis. The lesions found are of two kinds: (a) of the parenchyma; (b) of the interstitial tissue, in the form of the submiliary nodules described by Aschoff and Tawara, situated chiefly in the myocardium of the left ventricle.

Specific organisms were found in the nodules, some of which are found in the deep tissues of the valves, and from this it would appear that the organisms are carried to the valves by the coronary blood-stream, the valves becoming inflamed centrifugally and not centripetally. This inflammation results in the formation of blood-vessels in the valves. In consequence of this vascularisation of the valves, each successive attack of rheumatism renders the valves a more easy prey to inflammation; and this inflammation, when it has cooled down, results in fibrosis; so that each successive attack of inflammation increases the thickening and deformity of the valve in geometrical progression, by adding to the fibrosis, and also by increasing the number of blood-vessels still further. The question as to how non-vascular structures, such as the heart valves, become infected through the coronary blood-stream is a little difficult to explain. But that non-vascular structures do become invaded by micro-organisms is a fact, for the *Spirochaeta pallida* is found in the cornea in cases of congenital syphilis.

The point I wish to emphasize is that in rheumatic carditis the pathological basis of prognosis depends upon a demonstrable inflammatory lesion, as compared with the anatomical basis in other non-inflammatory lesions, such as aortic disease.

*The Age Incidence of Articular Rheumatism and its bearing  
on Cardiac Manifestations.*

As prognosis depends very largely upon the early recognition of the disease and its appropriate treatment, a few words must be said about the aetiology of acute rheumatism.

The manifestations of the disease differ very much with age, and, speaking generally, the older the patient the more marked are the articular lesions and

the less marked are cardiac manifestations. In children the reverse is true, for few attacked with rheumatic fever below the age of 16 escape without some damage to the heart, whereas the articular lesions may be very slight or altogether absent.

The frequent absence in children of definite articular lesions is a most unfortunate thing, for the febrile attack is often very mild, and consequently little notice is taken of it by the parents. The result is probably that the child is not confined to bed, but is up and about, thereby throwing unnecessary work upon the heart during the time that the rheumatic poison is circulating in the child's blood. The result is that the heart has not the same chance of resisting the poison as if it were doing its minimum of work, that is, when its owner is in bed, and consequently becomes irreparably damaged before any one is aware that the child is really ill.

The presence of rheumatic subcutaneous nodules has a definite bearing on prognosis, and when present, especially in children, are always accompanied by gross damage to the heart. They are very much more common in children than in adults, and are of much more serious significance. They may last for weeks or months, and when present constitute foci of infection, rendering the patient more liable to fresh attacks of rheumatism.

#### *Analysis of Cases.*

The in-patient records of 133 patients with rheumatic fever have been looked up. These cases extend over a period of six years—1903–1909 inclusive. The cases admitted to the Radcliffe Infirmary, Oxford, during the year 1911 have also been collected, and these two groups will be considered separately.

A certain number of the records looked up are so incomplete as to be of little or no value from the point of view of this essay; they have therefore been omitted from the analysis. This leaves 104 cases, whose records are analysed in the table following:—

TABLE I.

Group.	Age.	Sex. 1st Attack.		1st Attack, Rheu- matic Fever only.	Percentage of total number.	Morbus Cordis re- cent—cleared up before patient left Hospital.	Morbus Cordis re- cent—not cleared up on leaving Hospital.	No clinical signs of Morbus Cordis throughout the attack.	Condition of Heart in 1st attack not known.	Deaths in acute stage.
		M.	F.	Total.		Class A.	Class B.	Class C.	Class D.	
1	1-9	7	6	13	12.5	—	3	4	6	—
2	10-19	18	31	49	47.1	6	25	11	7	2
3	20-29	11	10	21	20.1	4	9	6	2	—
4	30-39	5	7	12	11.5	2	7	3	—	—
5	40-49	2	4	6	5.7	—	2	4	—	—
6	50-59	—	1	1	0.96	—	1	—	—	—
7	60-69	1	—	1	0.96	—	—	1	—	—
8	70 & over	1?	—	1?	0.96	—	—	1	—	—
Total		45	59	104	99.78	12	47	30	15	2

There are several points of interest in this table.

1. *Age and Sex Incidence.* The largest percentage of the cases, that is, 47·1 per cent., occurs between the ages of 10–19 inclusive. This agrees on the whole with Church's figures (5); he gives 43·5 per cent. in a series of 943 cases.

Of the forty-nine cases in this decade, nearly twice as many females were attacked as males, the figures being eighteen males and thirty-one females. A comparative table of age incidence is given below, the figures of Church being compared with mine.

TABLE II.

*Age Incidence.*

	Church's figures. 943 cases.	104 cases in my series.
Below 10 years	13·9	12·5
Between 10–19	43·5	47·1
"    20–29	25·6	20·1
"    30–39	13·5	11·5
Over 40	2·43	8·5

This table would seem to indicate that the percentage is fairly constant, whether taking a large or a small number of cases.

*Sex.* In this series of 104 cases, 45 males and 59 females were affected with rheumatic fever, the preponderance of females being 13·5 per cent. This is contrary to the general rule, though it is known that the numbers differ within wide limits. The explanation of these figures is, I think, that all ages have been grouped together, the result being misleading. If one excludes the cases in decade 10–19, during which period the disease is more common in girls, the figures are practically identical, 27 males and 28 females being affected. In decade 10–19 (49 cases) 13 more females than males were attacked with rheumatism, the preponderance of females being 26·5 per cent. Cheadle (6) states that from 11 to 15 years of age girls preponderate in the proportion of 2:1.

2. *Incidence of Cardiac Manifestations.* With regard to this, my figures differ very widely from those of Church, as given in Allbutt and Rolleston's *System of Medicine* (5). Below is a comparative table between his series of 144 cases and my series of 104.

TABLE III.

Group.	Endocarditis present.	Church's 244 cases.	Series of 104 cases Carditis present.
1	Cases under 10	75 %	28·5
2	"    between 10–19	54·1	73·7
3	"    "    20–29	30·6	68·4
4	"    "    30–39	33·3	75·0
5	"    over 40	12·5	33·3

The discrepancy is probably due to the fact that in Groups 1–3 there are fifteen cases in my series in which the condition of the heart during,

and after, the first attack is not known. Church states that it is very rare for a child to escape cardiac damage below the age of puberty; yet in my series, of the seven cases in Group 1, four are known to have had no cardiac damage, for one of them returned with a second attack, the heart at the beginning of the attack being quite normal; and the other three have been examined recently, and in each case the heart was found to be undamaged.

In Group 2 (ages 10-19) the percentage of hearts involved is much larger than that given by Church. This can also, I think, be explained by the fact that he has counted endocarditis only, while I have included pericarditis, endocarditis, and transient murmurs due to myocarditis. The same remarks apply also to Groups 3, 4, and 5.

The percentage in Group 4 is surprisingly high, but the number of cases is only twelve, too small a number in which to work out an accurate or reliable percentage. All nine cases in the group, however, had very definite signs of cardiac involvement, though in at least four cases these signs were transitory, two clearing up before the patients left hospital, and two more being now quite sound. These cases are briefly reported further on.

#### *General Remarks upon Cases recently examined.*

Of 133 patients whose records have been looked up 110 have been written to, and of those who replied, sixty-four have been examined. Many of those written to have left the district or the county, and so cannot be traced. The condition of the remaining sixty-four up to the present time is given in the tables following. They are dealt with under two groups: (1) those treated in hospital during 1911 (sixteen cases); (2) those who have been in hospital with acute rheumatism from 1903-9 inclusive (forty-eight cases).

#### *Methods of Examination.*

The methods of examination have for the most part been restricted to the ordinary clinical methods of inspection, palpation, percussion, and auscultation, with an examination of the pulse, the object being to find out as far as possible the size of the heart, its rapidity of action, and the condition of the valves. Where possible, also, an attempt has been made to determine the condition of the myocardium, and for this purpose the patients have been made to do dumb-bell exercises, sufficient to raise considerably the pulse-rate and quicken and deepen the respirations. In a certain number of cases, also, an attempt has been made to measure the efficiency of the heart by one of the special experiments devised for this purpose.

The results so obtained have been compared with the condition as found in the hospital records, and conclusions drawn from the comparison.

The condition of the myocardium has been judged more from the point of view of its physiological efficiency than from any clinical physical sign;

or, in other words, the patient's capacity for work has been taken as the criterion of his cardiac efficiency, and whether in the case of adults he can do as much work as he could before his attack of acute rheumatism.

1. *Cases of Acute Rheumatism treated during 1911.*

Total number, 20.

Of this number 14 were first attacks ;

3 were second attacks ;

3 were third or more attacks.

- |   |   |
|---|---|
| (i) Cases which ran the whole course of the disease without any clinical sign of heart disease . . . . .    | 1 |
| (ii) Cases which had cardiac lesions from a previous attack . . . . .                                       | 4 |
| (iii) Cases which developed signs of carditis in hospital, signs still being present on discharge . . . . . | 6 |
| (iv) Cases which developed signs of carditis in hospital, but had none remaining on discharge . . . . .     | 9 |

From these figures it will be seen that 45 per cent. of the cases showed definite signs of cardiac mischief, but completely cleared up before leaving hospital.

Most of these cases developed a definite mitral systolic murmur, with ventricular dilatation; some had no actual murmur, but a prolonged and altered mitral first sound, with or without irregularity of the pulse; while one case had a persistently rapid pulse (96-116) on being allowed up.

I have been able to examine sixteen of the twenty cases since their discharge from hospital. Of these the youngest is 10 years, and the eldest 34 years, the average age being 19.4 years. All have shown signs during the acute attack of old or recent carditis.

Six of the sixteen, recently examined, now have no sign of heart disease. Five others have lost their murmurs, but still have some prolongation of the mitral first sound. One case, who developed signs in the acute attack and cleared up before leaving hospital, has since developed a definite mitral regurgitant murmur.

These cases are briefly reported below :—

*Case I.* J. B., male, aged 33; first attack. Admitted Feb. 18, 1911, with acute polyarthrititis. Heart normal on admission. In a few days the apex was displaced outwards  $\frac{1}{2}$  inch in fifth space. Doubtful systolic mitral bruit. Mitral first sound blurred and prolonged all through the attack. Discharged April 5, 1911. Mitral first sound still impure.

Examined April, 1912. Apex beat in fifth space well inside nipple line. Heart normal in size, sounds quite clear and natural all areas. Doing full agricultural labourer's work for nine months without any discomfort.

*Case II.* A. C., female, aged 12; first attack. Admitted Feb. 6, 1911, with pain in back and chest lasting one week. On admission was suffering

with acute pericarditis; friction over base of heart and mitral systolic bruit, conducted upwards towards the pulmonary area. Pulmonary second sound much accentuated. Area of cardiac dullness increased upwards and to the right, not much enlargement to the left, apex being in the fifth space in the nipple line. The child made a good recovery and left hospital on April 1, 1911. Examined eight months later, heart was normal in size; a very faint mitral systolic bruit was heard after exertion. Patient then in good health.

Examined twelve months after attack, no murmur was heard at all, either at rest or after exertion. Child is in excellent health, plays games and drills at school. The dilatation and systolic murmur in this case were undoubtedly due to toxic weakening of the muscle and stretching of the mitral ring.

*Case III.* L. G., female, aged 10; first attack. Admitted March 30, 1911, with pains in limbs and erythema nodosum. Temperature  $101^{\circ}$ – $102^{\circ}$  F. Area of dullness increased to the right, and apex displaced  $\frac{1}{2}$  inch outside nipple line. Mitral first sound prolonged and indistinct. Pulmonary and aortic second sounds sharp and accentuated. On leaving hospital on May 2, 1911, the heart rhythm was a little irregular; mitral first sound still blurred, but no actual murmur.

On examination twelve months later, heart was normal in size, sounds clear and natural, rhythm regular. The child was well and healthy—went to school and played like other children.

*Case IV.* L. B., male, aged 21. Admitted April 13, 1911, with his first attack of acute rheumatism. On admission cardiac dullness not increased; mitral first sound blurred and indistinct, no actual murmur. Five days later a definite systolic murmur was heard, conducted into the axilla. Six days later the murmur was musical in character, the apex being still  $\frac{1}{2}$  inch inside the nipple line. Ten days later the murmur had lost its musical character and was not conducted so far out, not more than 2 inches from the apex. Four weeks later no murmur was heard even after a rapid walk up the ward. The apex was  $\frac{1}{2}$  inch further in towards the middle line. Pulse for the first few weeks was slow and intermittent, 50–80 per min. Left hospital May 30, 1911, pulse regular, 82–96 per min.

Examined ten days later, heart as on discharge. Had not been examined since, but was in good health, and earned his living as a waiter.

*Conclusion:*—The musical murmur was probably caused by vibration of the 'fluid vein' as pointed out by Gee. Although the amount of dilatation in this case was never very great, it was apparently sufficient to cause the murmur.

*Case V.* T. D., male, aged 30. Admitted Jan. 4, 1912, with second attack of acute rheumatism. On admission, apex was in the fifth space internal to nipple line. Mitral first sound impure. Pulmonary second sound reduplicated. Ten days later there was a definite soft systolic murmur conducted into the axilla. In four weeks' time the murmur had disappeared. Left hospital Feb. 21, 1912. Examined two months later, heart quite sound. Was then going to resume work as a labourer.

The following three cases developed heart signs in the acute attack, and though not quite cleared up, are very much better.

*Case VI.* E. C., female, aged 18. Admitted June 6, 1911, with first attack of acute rheumatism. Heart sounds and size normal on admission. A few days later mitral first sound became blurred and muffled. This persisted till discharge on July 26.

Examined nine months later, mitral first sound was a little prolonged; otherwise the heart was normal. For six months patient had been working as a general servant.



*Case VII.* W. K., female, aged 16. Admitted Oct. 11, 1911, with fourth attack of acute rheumatism. Heart sound on admission. In the course of a few days she developed a loud systolic mitral murmur, conducted into the axilla; there was considerable dilatation, apex being well outside the nipple line. The patient was very ill and had delusions, which were made worse by salicylates. Dilatation very gradually diminished, but the murmur was still present when she left hospital on Dec. 9, 1911, eight weeks after admission.

Examined four months later, was in good health, and had been doing housemaid's work for some months. No murmur was detected while at rest, but on exertion a very faint systolic murmur was heard, conducted  $1\frac{1}{2}$  inches from the apex, in fifth space. Apex well internal to nipple line. The pulmonary second sound was a little accentuated.

Whether the murmur in this case is of valvular or myocardial origin is, I think, difficult to say. It would be interesting to see this girl again at the end of, say, two years, and see if she has still got the murmur.

*Case VIII.* E. G., female, aged 26. Admitted Nov. 6, 1911, with first attack of acute rheumatism. On admission apex was internal to nipple, and no dilatation was made out. There was a soft mitral systolic murmur conducted into the axilla—pulmonary second sound not accentuated. On discharge, Dec. 2, 1911, the murmur was unchanged, except that it was not conducted so far out.

On examination four months later, apex was in the left nipple line; no increase in cardiac dullness upwards or to the right. Mitral first sound was a little prolonged, but there was no murmur. Had been doing full work as a general servant for two months.

The following case developed signs of recent carditis during the acute stage, but left hospital with normal heart sounds, and a pulse of 100–110. She became pregnant just before the attack, and when examined at the sixth month had a definite systolic mitral murmur.

*Case IX.* E. B., female, aged 20. Admitted Sept. 16, 1911, with second attack of subacute rheumatism. Heart not affected after the first attack, two years ago. On admission, apex was in fifth space in the left mid-clavicular line; mitral first sound muffled, pulmonary second sound short and sharp, aortic first weak and blurred. On leaving hospital on Oct. 11, 1911,  $3\frac{1}{2}$  weeks later, sounds were normal, but pulse was 100–110 per minute.

Examined six months later, patient had a soft blowing systolic murmur, conducted a short way towards the axilla, and heard at the pulmonary area. Aortic sounds natural. Apex still displaced a little to the left.

The myocardium in this case, already weakened by the rheumatic virus, had not time to recover before extra work was put upon it by the pregnant condition of the patient. As a result, the dilatation had not subsided, and the mitral valve was still relatively incompetent.

Of the other seven cases, one who had a persistently rapid pulse during convalescence still has tachycardia, pulse being over 100. He can, however, do more work than before his attack, and is in all ways perfectly healthy, so that probably his tachycardia is a normal phenomenon.

The other six have all got signs of valvular disease, but with good compensation. In one of these cases the murmurs have shown an alteration:—

*Case X.* E. M., male, aged 20. Admitted with first attack (subacute) on April 22, 1911. Heart was then unaffected. He very soon developed a mitral systolic murmur conducted into the axilla; also an aortic systolic. The apex-beat was never displaced outwards as far as the nipple line. He was sent out with the diagnosis of mitral regurgitation.

Examined eleven months later, the area of cardiac dullness was normal; apex inside nipple line. The mitral first sound was loud and prolonged, but no murmur was heard even after exertion. The aortic systolic murmur was brought out with exertion. He was working as a railway carman, without any heart symptoms, and looked and felt in good health.

## 2. Analysis of Cases admitted from 1903-9 inclusive.

This series comprises fifty-four cases, of which forty-eight have been recently examined, and six have died. All the cases examined have left the hospital well over two years ago, and from a study of these cases it is hoped that some idea of their after-history may be arrived at. A tabular list of these cases is given below, and requires a few words of explanation.

TABLE IV.

Group.	Age on admission to Hospital.	Sex.		Total.	Attack.			Severity.		Deaths.
		M.	F.		1st.	2nd.	3rd.	Acute.	Sub.	
1	10-19	6	16	22	11	7	4	13	9	4
2	20-29	5	5	10	6	2	2	8	2	—
3	30-39	3	6	9	1	5	3	3	6	2
4	40-49	3	5	8	5	—	3	1	7	—
5	50 and over	4	1	5	3	—	2	1	4	—
Totals		21	33	54	26	14	14	26	28	6

In the first place, no case in the series is below the age of 10 years. The oldest case (Group 5) is a man, aged 71, who is said to have had a subacute attack seven years ago. It is doubtful if this was really an attack of true rheumatism, and not a case of osteo-arthritis. He now has much deformity of the left knee, the joint most affected at the time.

As would be expected, the great majority had their rheumatic fever between the ages of 10-19 (Group 1). This decade also supplies, absolutely and proportionately, the largest number of first attacks, and also the most acute cases. With advancing age comes a lessening in the severity of the attacks, as well as a rapid decrease in their number, pointing to the fact that acute rheumatism is essentially a disease affecting those in the first half of life.

As seen in Table I, so also is it shown in Table IV, that in the Oxfordshire district females are more often affected than males.

The deaths must be dealt with in detail. In Group 1 two died during the acute disease :—

(i) Female, aged 19, of pneumonia and hyperpyrexia, developing during the course of the disease.

(ii) Female, aged 16, of coma, three weeks after the onset. There is no note of an autopsy in either of these cases.

The other two cases in Group 1 both died of heart disease :—

(iii) Female, aged 19, of 'malignant endocarditis and abscess of the spleen', three years after her third attack. There is no note as to the date of her first attack.

(iv) Male, aged 14, of 'heart disease', two years after his first attack at the age of 12. During his last two years he had scarlet fever, followed by a fresh attack of rheumatism, this being a frequent occurrence, as pointed out by Poynton.

The other two cases were adults :—

(v) Male, aged 40, apparently of myocardial failure, from the history, though I could get no reliable information on the point. He had his first attack at the age of 27, and his second (subacute) at the age of 35.

(vi) Male, aged 37, of 'heart disease and dropsy'. He had his first attack at the age of 24; second at the age of 33, and his third at the age of 34, dying three years later. After the last attack he had mitral and aortic regurgitation.

The general condition of the heart in the remaining forty-eight cases is given in the table below.

TABLE V.

Class.	Number of Cases.
A. Morbus Cordis present on leaving hospital, now quite cleared up	11
B. Morbus Cordis still present, but partially cleared up . . . . .	7
C. Morbus Cordis present. Heart <i>in statu quo</i> . . . . .	8
D. Heart worse than on discharge . . . . .	10
E. No Morbus Cordis throughout . . . . .	12
Total	48

The cases in Classes A and B are the ones upon which I wish to lay most stress. It will be best, therefore, to review briefly those in Classes C, D and E, and then consider Classes A and B more in detail.

Of the eight cases in Class C, seven have definite valvular disease, mitral or aortic, or a combination of the two. Two cases have mitral incompetence and stenosis together, just sufficiently compensated to allow them to do light work: both had their first attack before the age of 10.

Two cases have well-compensated mitral regurgitation, and both can do full work without ill effect, one as a general servant, the other as a housewife.

One has well-compensated mitral stenosis, and has had no symptoms of failure since her attack  $2\frac{1}{2}$  years ago. She is a school teacher, aged 39.

One case has mitral regurgitation with perfect compensation, and double aortic disease. Has remained well and at work in the Clarendon Press for  $9\frac{1}{2}$  years without any symptoms.

The remaining case has a persistent pulmonary systolic murmur, lasting now more than 10 years. She earns her living as a hawker.

Of those in Class D (10 cases) five have had recurrences of rheumatic fever, with further damage to the valves in four cases, and to the myocardium alone in one case.

Two cases, both subacute, in men over 60, show well-marked signs of atheroma of the aorta with high blood-pressure and ventricular hypertrophy, though they had no signs during their attacks.

One case, a girl, aged 18, though she has had no fresh attack and has no organic murmur, gets signs of myocardial failure at times, with dilatation and a mitral systolic murmur conducted into the axilla.

One case, a woman, aged 48, has had a second attack, and now suffers with signs of slight myocardial weakness. The mitral first sound is indistinct, and the pulmonary second sound is accentuated. She works in a blanket-weaving mill, and cannot do as much as she did before her second attack.

One boy, aged 13, had his first attack at the age of 11, without heart

involvement, and now has a pulmonary systolic murmur and a prolonged mitral first sound. He gets short of breath when chaff-cutting.

In Class E (12 cases) the average age is 35 years, the oldest being 43 and the youngest 15. Both these two cases had their first attack at the age of 9 years, and both have gone through second attacks without any disease of the heart. Seven of these twelve cases have had more than one attack, mostly subacute. The heart in every case is quite normal on examination at least two years, and in some cases up to nine years, after leaving hospital.

In Class B there are seven cases, which, although still presenting signs of heart disease, have improved to a very large extent, either as regards—

1. Alteration in, or disappearance of, murmurs ;
2. Capacity for work.

Brief abstracts of six of these cases are given below :—

*Case XI.* A. E., female, aged 45. Admitted with third attack (subacute) on Dec. 2, 1903. First and second attacks at the ages of 11 and 15. Heart said to have been affected during the first attack. On admission, apex in fifth space, just outside left nipple line. Cardiac dullness not increased upwards or to the right. Well-marked presystolic thrill at apex, presystolic and systolic murmurs, the latter conducted to the axilla. On Dec. 4, loud pericardial friction heard over pulmonary base, which persisted till her discharge on Jan. 13, 1904. The double murmurs were still present, though no thrill could be felt.

On examination in April, 1912, over eight years later, there was no thrill, the apex was still displaced a little outwards and a crescendo presystolic murmur ending in a 'sail-flap' first sound was heard, but there was *no systolic murmur*, either at apex or other area. The pulse was intermittent, and there was systolic recession between eleventh and twelfth ribs at the back (Broadbent's sign). Functionally, her heart was in good condition. She did her own house-work, and also worked as a charwoman at the age of 53. She had no signs or symptoms of loss of compensation.

*Case XII.* G. F., female, aged 13. Admitted with second acute attack on June 5, 1909. First attack, aged 7. Cardiac dullness second left interspace, mid-sternal line, to apex, in fifth space, just outside mid-clavicular line. Pulsation all over praecordia. Presystolic thrill and murmur at apex, conducted inwards towards sternum. Mitral systolic murmur conducted to axilla. Pulmonary second accentuated. Pulse 108, low tension. On discharge, July 10, 1909, murmurs unchanged, faint thrill still felt.

Examined  $2\frac{1}{2}$  years later, apex was in same position, upper limit of dullness being at third left costal cartilage. A long blowing apical systolic murmur was heard, conducted into axilla. There was no thrill and *no murmur in diastole*. Pulse 86. Was idle for two years after her attack. Since then has done house-work and nursemaid's work. No symptoms or loss of compensation.

*Case XIII.* A. N., male, aged 13. Admitted May 25, 1904, with second acute attack, and pericarditis. First attack of acute rheumatism at age 7. Pericarditis with much dilatation, cardiac dullness being from third rib, 1 inch to right of sternum, to apex, in mid-axillary line. Systolic mitral bruit heard all through. Temperature on admission, 102.4° F. Pulse during the last week 98–104.

Examined  $7\frac{9}{12}$  years later, dullness was normal, apex being in fifth space, internal to nipple. Visible impulse from second to sixth space. No systolic retraction at apex, but Broadbent's sign was present behind at left costal margin. Mitral first sound was a little prolonged, but *no murmur was present*. Pulmonary

sounds normal. Probably a case of pericardial adhesions without cardiac embarrassment. Had no symptoms of any kind since his acute attack; earned his living as a glove-cutter, which entailed exertion in stretching leather; played cricket and football, and cycled eleven miles in from the country to be examined. Had been passed by two doctors for club and insurance.

*Case XIV.* J. S., male, aged 57. Admitted with fifth attack (acute) April 24, 1905. First attack at age 37. Apex-beat fifth space  $\frac{1}{2}$  inch outside nipple; mitral systolic bruit. Pulse last week in hospital 120-144. Went out June 10, 1905 with diagnosis of mitral regurgitation.

Examined seven years later, there was a doubtful mitral systolic bruit, not conducted from apex, and not constant. Sounds at other areas normal. Pulse 92, artery thickened (patient aged 64). Systolic blood-pressure 185 mm. Could not work as he was crippled with chronic arthritis of knees and shoulders.

*Case XV.* J. T., male, aged 21. Admitted with relapse from first (acute) attack, Jan. 26, 1906. Apex diffuse, third and fourth spaces, felt best in fourth space  $1\frac{1}{2}$  inches outside nipple line. Loud mitral systolic murmur, second sound absent. Pulmonary second sound increased. On discharge, diffuse forcible pulsation in third and fourth spaces as far out as anterior axillary line. Mitral murmur as before.

Examined  $6\frac{2}{3}$  years later, cardiac dullness was normal, apex in fifth space  $\frac{1}{2}$  inch internal to nipple. At mitral area both sounds were heard, with a short soft systolic bruit immediately following first sound; not brought out more on exertion. Worked as a coal porter, lifting one cwt. sacks and carrying them as much as 100 yards. Compensation had never failed, though he found the work too much for him at times. Was a medium-sized man.

*Case XVI.* H. G., male, aged 14. Admitted with second (acute) attack on June 4, 1905. First attack at age 7. On admission apex was  $\frac{1}{2}$  inch outside nipple in fifth space; mitral systolic murmur present.

When examined  $6\frac{2}{3}$  years later, apex was in fifth space, internal to nipple. Heart beat was forcible, and a little irregular. No definite murmur was heard at any area, though the pulmonary second sound was suggestive of a diastolic murmur. Mitral sounds were clear. Pulse rapid, 98-110.

Class A consists of 11 cases, all of whom have shown signs of carditis and have completely cleared up, leaving hearts quite sound physiologically.

7 of these had one attack.

2 " " two attacks each.

2 " " five attacks each.

Of the seven first attacks, four were between the ages of 10-19, and three between 40-56.

Both the patients with two attacks had their first below the age of 15.

These cases are briefly outlined below:—

*Case XVII.* R. B., female, aged 19. Admitted with first attack May 28, 1908. Temperature 101° F. Pulse 100. Heart became irregular, but no murmur was heard.

Seen four years later, heart absolutely normal, pulse regular. Did her own house-work, and glove-making with treadle machine. Had had no heart symptoms, and was five months pregnant at time of examination.

*Case XVIII.* H. C., male, aged 15. Admitted Jan. 19, 1908, with first (acute) attack. Apex displaced into nipple line. Impulse forcible; blowing systolic murmur over apex conducted to axilla. Twelve days later,



note reads:—'Rough mitral first sound—no definite bruit.' On discharge, Feb. 26, 1908, heart was said to be 'well compensated'. Examined April, 1912, over four years later, there was no sign of past cardiac damage. Worked nine hours a day as a market-gardener without ill effect.

*Case XIX.* M. M., female, aged 40. Admitted with first attack (subacute) in July, 1909. Developed a mitral systolic murmur, not conducted from apex, but remaining on discharge from hospital.

Examined  $2\frac{9}{12}$  years later, there was no sign of old or recent carditis.

*Case XX.* E. H., female, aged 56. Admitted with first attack (subacute) in August, 1909. Apex not seen or felt. Systolic murmur heard all over the præcordia, not conducted outwards from apex.

Examined  $2\frac{9}{12}$  years later, heart was normal in size, and no murmur was heard. Had been in excellent health ever since attack. Earned her living as a midwife, attending as many as 100 cases a year.

*Case XXI.* G. S., male, aged 11. Admitted with first acute attack on Sept. 16, 1905. Heart a little enlarged, apex in fifth space in nipple line. Pulmonary second accentuated. After three weeks he developed a systolic apical murmur, not constant. On Oct. 23, murmur became constant, and loudest at pulmonary area. Remained unchanged till he left hospital on Jan. 10, 1906. Was diagnosed as mitral incompetence.

Examined six years later, heart was normal in size, apex being in fifth space well inside nipple line. Sounds clear and valvular all areas. Worked as a groundsman—mowing, rolling, &c. Played cricket and football, and hoped soon to play county cricket. No return of rheumatic symptoms since attack in 1905.

*Case XXII.* J. F., male, aged 45. Admitted with first attack (acute) in March, 1908. Cardiac dullness not increased, apex not displaced. Blowing mitral systolic murmur heard, which cleared up before discharge four weeks after admission. Had remained well, doing full work as a house-painter and decorator for four years. Heart found to be quite sound.

*Case XXIII.* G. F., male, aged 14. Admitted Feb. 22, 1908, with first (subacute) attack. Apex in nipple line, cardiac dullness increased to the right. At apex 'a blowing systolic bruit, preceded by a distinct rumble' (note). On March 14, 1908, note reads: 'There is a suggestion of a thrill or palpitation,' and a 'distinct rough sound preceding mitral first'.

Examined four years later, no sign of heart disease could be found. At the age of 18 had been doing heavy work in a steam laundry, stoking the furnaces, pushing trucks, &c., for twelve hours a day. Gave up this work for a lighter billet as greaser on G.W.R. wagon-sheds, as he had 'a touch of the rheumatics again'. Heart had been passed for the Royal Navy by three doctors.

*Case XXIV.* E. B., female, aged 14. Admitted with first attack of acute rheumatism in Jan. 1901. Note on the heart says: 'Mitral first sound long; no murmur; pulmonary second sound accentuated'. Second acute attack in 1909, at age 23. Temperature 102° F. Pulse 96–118. Apex-beat displaced to the left. Systolic murmur at apex conducted as far as the mid-axillary line. Pulmonary second sound increased.

Admitted a third time in March, 1911, with tuberculous pleurisy. On careful examination no physical sign of disease was found in the heart, which was normal in size, and sounds were clear in all areas. Had had no cardiac symptoms since second attack, and had been doing general servant's work.



*Case XXV.* K. M., female, aged 15. Admitted with second attack (acute) on August 4, 1904. No note as to date of first attack. Heart dullness normal, apex fourth space 3 inches from mid-line. Soft blowing systolic bruit heard at apex.

Seven years later was admitted with gonorrhoeal vaginitis, August, 1911. No sign of any cardiac lesion, old or recent.

*Case XXVI.* E. C., female, aged 34. Has had four subacute attacks since the age of 30. Fourth attack, March, 1903, during which she had blurring of the mitral first sound, but no actual bruit. Fifth attack two years ago (1910).

Examined April, 1912, showed no signs of old cardiac involvement.

*Case XXVII.* W. C., male, aged 27. Admitted March 15, 1905, with fifth attack of acute rheumatism. Developed a mitral systolic murmur; no note as to its conduction. Discharged himself after three days. Came up six years later for salvarsan treatment. Heart at that time was quite sound, and has remained so since the treatment. Had been working on a newspaper press for many years.

#### *The Estimation of the Efficiency of the Cardio-Vascular Mechanism.*

Several methods have been devised in the attempt to gauge the efficiency of the heart as a pumping-machine, and to test the reserve power of the heart muscle. I have done experiments in twenty-three cases, using the method described by Graupner and reported on by Cabot and Bruce (10).

The method consists in making the patient do a measured amount of work, after taking the pulse-rate and maximum systolic blood-pressure at rest. This work is done by making the patient climb stairs to a known height, and computing the work done in foot-pounds per minute, each patient, as far as possible, doing about the same amount of work. The work done is found by multiplying the patient's weight in pounds by the height in feet through which he has raised this weight. The pulse-rate and blood-pressure are then taken every two minutes until both have again reached their normal.

Graupner found that in a healthy young adult, after the performance of a moderate amount of work, the pulse rises suddenly, and again drops rapidly to normal. The blood-pressure, on the other hand, rises slowly and does not reach its maximum until six or eight minutes after the work has been done, and some time after the pulse has dropped to its normal state. His experiments are corroborated by Cabot and Bruce (see Chart I).

In the case of a seriously weakened heart muscle, the 'Erholung' (as Graupner terms the reaction) is less marked, the pressure rising and falling again to normal much more slowly.

In a very seriously weakened heart the pressure may fall immediately the work is done, and take some time to rise to its normal again (see Chart II).

My series of experiments with this test comprise seventeen rheumatic fever patients, fifteen of whom showed at some time signs of cardiac involvement, three cases at least having considerable cardiac weakening at the time of

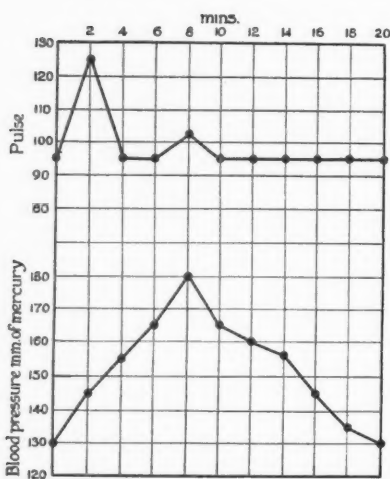


CHART I. Work done = 6,200 ft. lbs. in 1 min. From a healthy adult, aged 24. Cabot and Bruce find this to be the commonest type of curve in normal healthy adults (Cabot and Bruce).

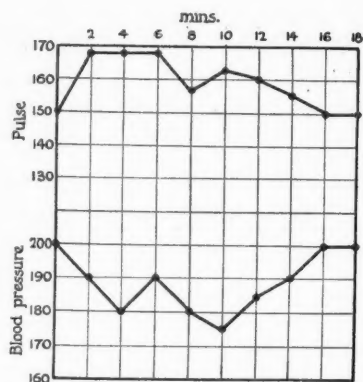


CHART II. Walked 40 yards. Case of ruptured compensation, myocarditis, cyanosis, &c. Patient, aged 48, was too ill to climb stairs (Cabot and Bruce).

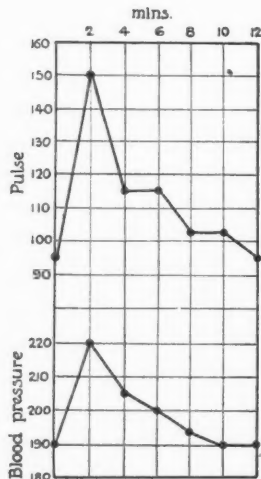


CHART III. 'Curves found in a number of more seriously weakened hearts in older persons with high blood-pressure.' Patient, aged 50. Arterio-sclerosis (Cabot and Bruce).

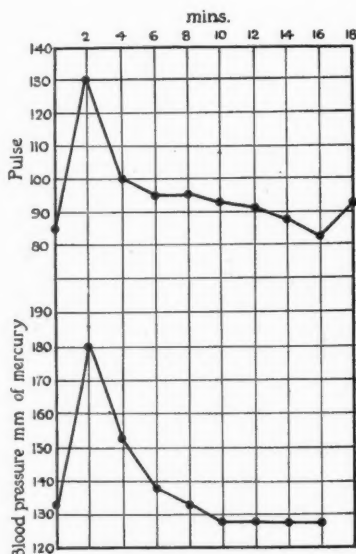


CHART IV. Average work done = 6,046 ft. lbs. in 1 min. Composite plotted curves of 17 rheumatic fever patients.

the experiment. The other six cases are controls, all being young healthy males—two Oxford undergraduates, one being a member of the Oxford University boat crew for the years 1911-12; two convalescent surgical patients; and two of the Resident Medical Staff of the hospital. None of these controls have had rheumatic fever, or scarlet fever, or any serious illness.

*In no case, healthy or diseased, in my series, has the blood-pressure risen in the way indicated by Graupner, and a composite plotted curve of the seventeen rheumatic cases shows no essential difference from that of the six healthy normals,*

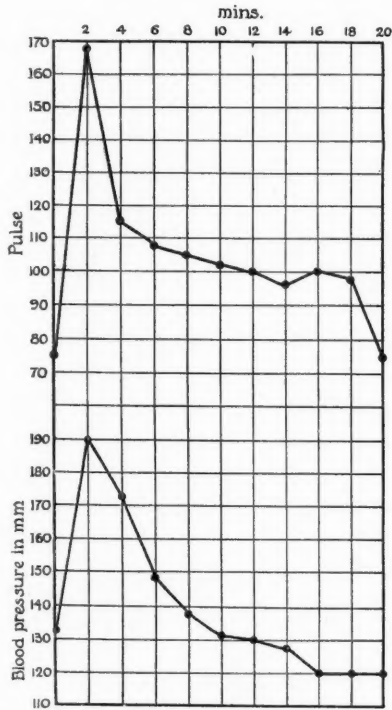


CHART V. Average work done = 10,000 ft. lbs. in 1 min. Composite plotted curves of 6 young healthy adults.

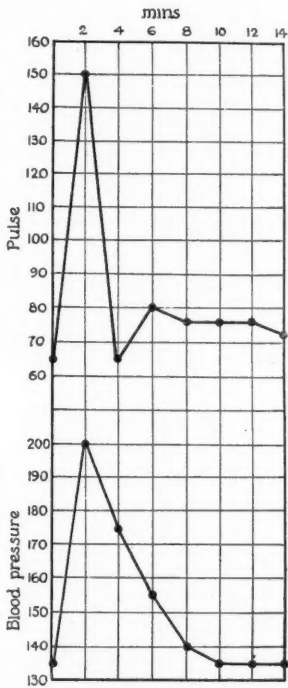


CHART VI. Work done = 13,000 ft. lbs. in 1 min. Chart of member of Oxford boat crew,  $3\frac{1}{2}$  weeks after the race of 1912.

as will be seen from the Charts IV and V. In fact, these two charts correspond closely to the reaction which Cabot and Bruce give for 'more seriously weakened hearts in old people with high blood-pressure' (Chart III).

A number of the most interesting charts of individual patients are given, with a short note on each: lack of space prevents the whole series being included.

The technique employed has been that described in Cabot and Bruce's paper (10), the sphygmomanometer used being a modification of Riva Rocci's

instrument. Except in one case, the stairs climbed were the same, and all experiments were conducted under similar conditions, the blood-pressure in all cases being taken by the writer, so that the experimental error is constant.

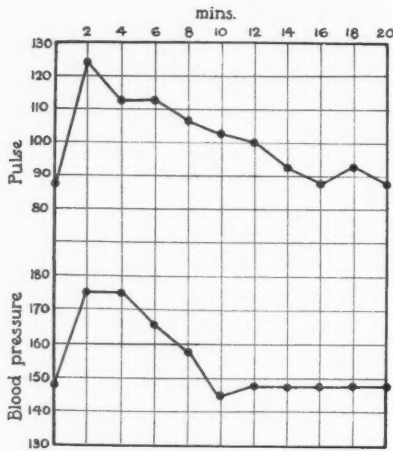


CHART VII. Work done = 5,760 ft. lbs. in  $\frac{3}{4}$  min. E. M., male, aged 21. 1st attack rheumatic fever, 1911. Heart temporarily affected; not completely recovered at time of experiment.

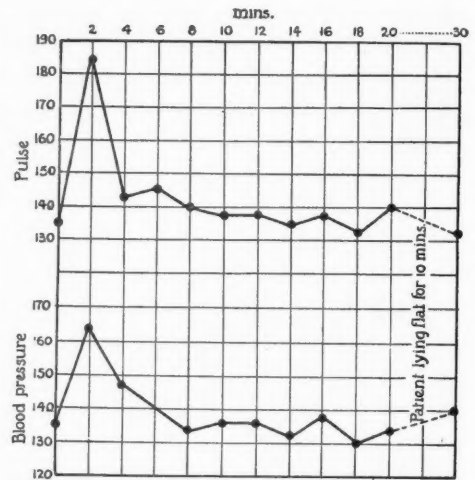


CHART VIII. Work done = 4,392 ft. lbs. in 1 min. A. B., female, aged 18 $\frac{1}{2}$ . Rheumatic fever, 1909, with carditis. Showed signs of early failure of compensation at time of experiment. Few weeks later compensation failed.

*Conclusions drawn from a Consideration of the Cases Analysed in this Essay.*

1. That 23 per cent. of patients go through one or more attacks of acute rheumatism without any clinical affection of the heart, irrespective of the age when first attacked.

2. That 22 per cent. develop signs of carditis in the acute stage, these signs disappearing during convalescence.

3. That 18-20 per cent. of the cases which develop signs of endocarditis, not clearing up before patient leaves hospital, have no permanent valvular lesion, the murmurs being due to myocarditis, or incompetence from temporary hyperaemia of the valves, associated with dilatation. If a synovial membrane can recover, why should not a heart valve?

4. That in 14.5 per cent. of cases with acute rheumatic endocarditis of severe type, the murmurs undergo a change, resulting in the disappearance of one or more of the murmurs, such murmurs being due to associated dilatation.

5. That, as a rule, the murmurs due to myocarditis are softer in character than those due to valvular disease.

6. That cases in which the heart is going to recover completely show signs

of such recovery within twelve months of the acute attack, though the process may not be completed till some years later.

7. That Graupner's test for the estimation of the cardiac efficiency has not been proved to be of any value in enabling one to recognize the presence or degree of cardiac weakening, not appreciable by the methods already in general use. The amount of physical work which each individual can do in earning his or her living is a far more reliable and efficient test of the heart's working capacity.

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## CRITICAL REVIEW: ANAPHYLAXIS AND ITS BEARING ON MEDICINE

By JAMES McINTOSH

THE course of certain diseases, and in particular those of the nature of an acute infection, is marked by the appearance of a well-defined series of symptoms, the exact significance of which were until quite recently only surmised. The discovery of a micro-organismal cause for many of these, together with the principles of anaphylaxis, has cleared up most of the mystery concerning the origin and nature of these manifestations. It is with the latter that this article is concerned.

Many instances of anaphylactic phenomena have been known to medical science for some considerable time, although their true significance was not understood. The early workers on the transfusion of blood noted that second injections were often followed by toxic, if not fatal, symptoms. Again, Jenner's observation of the shortened incubation period in revaccination is another instance.

Like many medical advances, anaphylaxis was not the discovery of a single genius, but has had a gradual evolution. The history of the condition dates from the discovery of artificial immunity. Koch, in 1890, clearly showed that tubercular guinea-pigs were more susceptible to an injection of tubercle bacilli than were normal guinea-pigs; while his demonstration of the tuberculin reaction was the first practical application of anaphylaxis in diagnosis. Von Behring, working on antitoxic sera, noticed that second injections invariably caused greater toxic manifestations than the first. The introduction of diphtheria antitoxin into general use, and the resulting 'serum sickness', led to an inquiry into the subject and its subsequent evolution. Richet, in 1902, introduced the term 'anaphylaxis' to explain certain phenomena of hypersensitivity observed in dogs which had received injections of actino-congestin, a tox-albumin. Then, in 1903, von Pirquet's observations on vaccination, revaccination, and 'serum sickness' not only placed the subject of anaphylaxis on a firm basis, but gave a good theoretical explanation of the condition.

That toxic symptoms should follow a reinjection of serum when nothing abnormal occurred after the first was a very difficult problem for the earlier workers. According to their preconceived views an injection of bacteria or their toxins in a non-lethal dose protected against a much larger and even fatal dose. But in the instance cited an injection of serum rendered the animal more susceptible to further injections than a normal animal. It was inconceivable that any



injurious substance could result from the interaction of an antibody and its antigen (albumin injected). An injection of toxic bacteria, such as typhoid bacilli, led to the formation of antibodies, agglutinins, precipitins, &c., and injections of toxins to antitoxins, antisubstances which destroy or neutralize the noxious materials.

What, then, is the nature of the so-called anaphylactic or hypersusceptible state? As we shall see later, it is very probable that the first injection of serum leads to the production of an antibody (an anti-albumin), so that when a second injection is made the serum introduced into the system unites with the antibody, with the result that a toxic substance is produced. An anaphylactic reaction is therefore, in the true sense of the word, an immunity reaction.

Anaphylaxis may therefore be said to be a condition of hypersensitiveness to a substance of an albuminous nature, existing normally in an animal, or induced as the result of a previous injection or injections of the albumin. An individual may therefore have a natural or artificial hypersensitivity to an albuminous substance: the former of these two states is also called an idiosyncrasy, but, as we shall see later, there is reason to believe that idiosyncrasy to drugs is not of the same nature.

#### *The sensitizing substance or Antigen.*

The essential constituent of a sensitizing injection is an albuminous compound.

Anaphylaxis has been produced to tox-albumins, such as actino-congestin, ferments, animal albumins, milk, egg-white, various sera, organ extracts, plant albumins, such as pollen, cocoa butter, and bacteria or bacterial substances. Certain workers claim to have sensitized animals to substances of known chemical formula, but later researches have failed to confirm this. As bacteria or their products are capable of acting as antigen, all diseases of microbic origin are involved in this subject. The antigen, therefore, may consist of dead (serum disease, hay fever, &c.) or living (all infections) proteid.

#### *Experimental Anaphylaxis.*

Experimental anaphylaxis really begins with the researches of Richet and Portier on the toxicity of actino-congestin, a tox-albumin extracted from the tentacles of sea anemones. In 1902 these writers found that dogs were extremely susceptible to a second injection of this tox-albumin.

The active principle extracted was called actino-congestin, the minimum lethal dose of which averaged about 0.078 gm. per kilogram of body weight for a primary injection. Death usually occurred within twenty-four hours of the giving of the toxin, with characteristic lesions, marked congestion of the gastro-

intestinal canal, with haemorrhages into the bowel, pleura, and pericardium, hence the name.

In their experiments a non-lethal dose was injected, and then after an interval of some twelve days a second non-lethal dose was injected. A dog thus treated usually dies a few minutes after the second dose, and in some cases as minute a dose as 0.001 grm. per kilogram of body weight is sufficient to bring about a fatal result. Immediately after the reinjection dyspnoea occurs, which is followed by vomiting, diarrhoea, rectal tenesmus, and increased heart action. Ataxia, if not actual paralysis, is followed by unconsciousness and death. Recovery may occur, however, even after unconsciousness has supervened.

An autopsy on a dog which had died during an acute attack showed a congestion of the gastro-intestinal tract with interstitial haemorrhages. The lungs as well as the other viscera were congested.

Richet also found that extracts of the muscles of the edible muscle (*Mytilus edulis*) yielded a tox-albumin similar in action to actino-congestin, which he called 'mytilo-congestin'. More recently he found that the sap of certain plants possessed similar toxic properties, in particular that of the *Euphorbiaceae*, *Hura crepitans*, the active principle of which he called 'crépitine'.

Arthus, in 1903, observed that repeated injections of normal horse serum, a serum non-toxic in itself, produced in rabbits a reaction on the part of the animal to the serum. Infiltrations were found to occur at the inoculation sites, though they were not noted after the first or second subcutaneous injections. In fact, the greater the number of inoculations the more marked was the infiltration and the more rapidly it formed. After the seventh injection of horse serum so severe a reaction occurred that necrosis of the tissues followed. He also observed that an intravenous injection of horse serum in a rabbit previously treated with serum produced immediate toxic symptoms. At the onset of these the rabbit lies down at full length on his abdomen and breathes rapidly, while evacuations of urine and faeces may occur. In a few instances, after one or two severe spasms of the diaphragm, the animal cries out and collapses, and on examination is found to be dead (Arthus phenomenon).

Arthus obtained similar results with sterilized milk, and found that the sensibility of the rabbits to repeated injections of horse serum or milk was specific.

At the same time von Pirquet and Schick, after a series of observations on man, came to the conclusion that the toxic phenomena occasionally observed after injections of horse serum were of an anaphylactic nature. Unlike Arthus, who considered that the repetition of the injections was the chief factor in the increased toxicity, they said that the reaction was of the nature of an immunity reaction, and founded their theory of the incubation period on it.

Theobald Smith, in 1904, while standardizing diphtheria antitoxic serum by means of guinea-pig injections, found that injections of diphtheria toxin previously neutralized by excess of antitoxic serum produced severe, if not fatal, symptoms in guinea-pigs which had been treated a month or so previously with a similar nontoxic mixture (Theobald Smith phenomenon).

It was Otto, however, who demonstrated that it was the horse serum in the mixture and not the toxin which played the active part. In the last few years the above observations have been largely supplemented and elaborated, with the result that we now possess a fairly exact knowledge of the condition, which I shall now attempt to give briefly.

Anaphylactic phenomena can be produced in most animals. A notable exception is the rat, and it is interesting to recall that rats are uninfluenced by electrical shocks which are immediately fatal to much larger animals. In the great majority of anaphylactic experiments guinea-pigs are used owing to their greater sensitivity. Unless otherwise mentioned the descriptions apply to anaphylaxis in the guinea-pig.

#### *Sensitizing Injections.*

The essential element in all sensitizing injections, as already stated, is an albuminous substance. These may be tox-albumins, animal or vegetable, such as actino-congestin and crepitin; animal albumins, milk, tissue extracts, egg albumin, various sera, and ferments; plant albumins, such as pollen, cocoa butter, bacteria and bacterial substances.

In most of the recent experiments injections of horse serum are usually employed, both on account of the facility with which it can be obtained and its ability to sensitize. The sensitizing injection of foreign proteid may be made intravenously, intracardially, intraperitoneally or subcutaneously, but as a rule they are made intraperitoneally. For experimental purposes, from  $\frac{1}{4}$  to  $\frac{1}{2}$  c.c. of serum is usually injected in the case of the guinea-pig, although a much smaller quantity may be sufficient. Rosenau and Anderson claim to have sensitized with as small a quantity as 0.000,001 grm. (crystallized albumin), but 0.001 to 0.04 c.c. will sensitize in most instances. Several attempts have been made to sensitize the animals by feeding them on foreign proteid given in excess, with indifferent results, most recent researchers denying that this is possible (Besredka). Rabbits as a rule are given from 1 to 4 c.c. subcutaneously and dogs 3 to 5 c.c. intravenously.

#### *Incubation Period.*

Before hypersensitivity can manifest itself a period of time must be allowed to elapse between the first and second injection. This period as a rule varies from six to twelve days, but it is greatly influenced by the size and site of the first injection; a large injection lengthens the period, as also does a subcutaneous injection. In the case of the rabbit several injections must be given before a high degree of hypersensitivity can be produced. In experimental work one always allows a period of at least ten days to elapse before giving the second injection.

*Duration of the Anaphylactic State.*

Once produced, the state of hypersensitivity may persist for a long time. In the guinea-pig Rosenau and Anderson found it still present three years after the first injection ; while in man Currie found the condition persisting for five years. But the duration of the condition is very variable, varying with the dose, the method of injecting, and the species of the animal.

*Production of the Anaphylactic Shock.*

A reinjection of serum in a guinea-pig, if given at least ten days after the first, will produce a train of symptoms now recognized as an anaphylactic shock. In the guinea-pig usually from 0.25 c.c. to 0.5 c.c. of serum injected intravenously is sufficient to bring on the reaction immediately, while larger animals such as the rabbit and dog require correspondingly more. If the injection is made intraperitoneally a larger dose is required. Besredka and Steinhart found that when the injection was made intracerebrally a minute dose only was required, in fact 0.0025 c.c. was sufficient.

*Symptoms of Anaphylactic Shock.*

Immediately, i.e. within thirty seconds, after an intravenous injection in a sensitized guinea-pig the animal shows marked excitement, moving from one place to another, lying down and then rising immediately. Usually it rubs its nose with its fore-feet and coughs occasionally. A few seconds later it falls down, and there are severe respiratory spasms with evacuation of urine and faeces. At times general convulsions may appear, or a condition of complete paralysis, the animal dying soon afterwards from respiratory failure. In the other laboratory animals the general symptoms are the same, though less pronounced as a rule.

In a post-mortem examination of an animal which has died of an anaphylactic shock, one notices that the blood is dark in colour and has little tendency to coagulate, while the heart has stopped in systole. The lungs are congested and voluminous. There is an increased peristalsis of the bowels, which are congested, and in their walls minute haemorrhages are to be found.

In guinea-pigs the respiratory changes are most marked: the alveoli of the lungs are dilated, while the bronchi are contracted. Auer and Lewis, who first described the condition, say that this contraction is so intense that it prevents air entering the alveoli and the animal actually dies of strangulation.

*Specificity.*

Within certain limits an animal sensitized to horse serum will only react to an injection of horse serum. Anaphylaxis, like other immunity reactions, is only relatively specific and not absolutely. In anaphylaxis the degree of specificity is difficult to determine, as a hypersensitized animal has an increased susceptibility to any toxin, and according to Uhlenhuth this fact should always be borne in mind in applying an anaphylactic reaction to medico-legal investigations. Gay and Southard and Arthus say that if an anaphylactic reaction has been provoked by a different serum from that used to sensitize the animal, the reaction is much less severe than that produced by a corresponding amount of a serum homologous to the sensitizing serum. In hypersusceptibility there is a group reaction, just as is the case with precepitins and agglutinins; thus an anti-human precepitin serum gives a precipitate with the sera of anthropoid apes, while a typhoid agglutinating serum agglutinates *B. coli* and *B. paratyphosus* to a less extent than it does the typhoid bacillus. A guinea-pig sensitized to horse serum will react slightly to an injection of goat's serum, while those sensitized to cow's milk will also react slightly with goat's milk, and as soon. But on the whole the reaction is highly specific. Perhaps the non-specific reactions are due to this increased susceptibility to various toxic substances, the injection of foreign proteid leading to an increased irritability of the whole nerve mechanism and, in particular, the vaso-motor system.

*Mechanism of Anaphylactic Shock.*

The most natural explanation of the acute intoxication of an anaphylactic shock was that it was due to a toxin acting on the animal organism. Richet in his writings termed the toxic substance apotoxin, and more recently Frieberger called it anaphylatoxin. Granted then that the second injection results in the formation of a toxin, on what system or systems does it act to produce the various phenomena known as an anaphylactic shock?

Besredka considers that the anaphylatoxin acts mainly on the central nervous system, the other phenomena being secondary to the intoxication of the brain. The nerve cells develop a high degree of susceptibility to the serum, as shown by the fact that an intracerebral injection is fifty times as toxic as an intravenous. Moreover, he demonstrated that the various anaphylactic manifestations could be prevented by a general narcotic.

In the dog, according to Biedl and Kraus, the most marked symptom is a fall of blood-pressure due to a loss of tone in the arterioles. The toxin, they believe, acts peripherally on the muscular fibres in the vessel wall, since adrenalin is without effect, while on the other hand barium chloride not only counteracts the fall but can prevent it.

In the case of the guinea-pigs the respiratory system is affected, and during the shock the bronchi become so much contracted that air is prevented from

entering the alveoli of the lungs and the animal actually dies of suffocation. Atropin given before the serum injection prevents to a great degree these lung changes, while section of the vagi, even when sufficient time was allowed for degeneration of the nerve ends to have taken place, was without any appreciable effect on the following shock. Auer and Lewis consider that the phenomena are of peripheral origin and due to a direct action on the unstriated muscle fibre.

The major phenomenon, therefore, varies according to the animal observed. In the rabbit the heart muscle seems mainly to be affected. In most animals, however, distinct fall of blood-pressure occurs, with a lowering of the body temperature. Biedl and Kraus consider that the preventive effects of anaesthetics is due to their rendering the brain insensible to the fall of blood-pressure and the resulting anaemia.

#### *Anti-Anaphylaxis.*

Otto observed that a sensitized guinea-pig which had survived an anaphylactic shock was immune to subsequent injections of serum. Besredka found that guinea-pigs which had been treated with minute quantities of serum subcutaneously during the incubation period showed no anaphylactic symptoms when injected later intravenously; one large dose, according to Rosenau and Anderson, has the same effect. But animals can be desensitized even after the incubation period has passed without the production of any symptoms, by the injection of very minute doses of the sensitizing serum. The condition, however, in many instances is not permanent, and the state of hypersusceptibility returns after a longer or shorter interval.

Certain drugs, such as barium chloride, and even hypertonic salt solution, lessen the shock if given previously to the administration of the serum, probably by causing a direct contraction of the muscle fibres in the walls of the blood-vessels.

#### *Passive Anaphylaxis.*

The serum of a rabbit or guinea-pig sensitized to horse serum if injected into a normal rabbit or guinea-pig will make that animal hypersensitive to an injection of horse serum. A latent period of at least four hours must have elapsed between the first and second injections before the reaction can be brought about. It is supposed that the serum must be given time to penetrate into the interior of the cells.

#### *Local Reactions: Allergie.*

For the most part we have been dealing with reactions of a general nature, in which the toxin is carried to the various parts of the body by the vascular system; on the other hand, there are anaphylactic reactions which are purely local. In the latter type of reaction characteristic histological changes are to be



observed in the tissues, but it must be remembered that there is no absolute demarcation between the two reactions, the one merging into the other. This type of reaction is more or less a localized cellular reaction.

Von Pirquet was the first to draw attention to the nature of these local reactions in medicine; he observed that when a reaction occurred at the site of an inoculation a second injection of the same albuminous material produced a much worse reaction. He cited vaccination (Jennerian) and revaccination as an instance of this. He termed this altered reaction power of the tissues 'Allergie'. As we shall see in a later part of this paper, his theory has helped to explain many peculiar reactions observed in acute infections which were otherwise inexplicable.

### *Theoretical Interpretations.*

Von Behring called these reactions, which we now recognize as anaphylactic, 'paradoxical reaction,' and believed them to be of a histogenic or cellular nature, as they were observed even when there was a large content of antibody in the serum. To this paradoxical reaction Richet later gave the name 'anaphylaxis', which means, 'against protection'. Ehrlich also favoured the cellular explanation of the reaction; the first injection stimulated the tissue cells to produce antibodies which, according to his side-chain theory of immunity, he terms 'receptors'. These receptors are at first anchored to the cell protoplasm, but later are cast off into the general circulation. But if a second injection be made before the receptors have been thrown off, the albumin-antialbumin reaction takes place inside the cell, which is the cause of the anaphylactic manifestations. A recent experimental work of Dale's adds some support to the above view, in which he demonstrated that the uterus of a sensitized guinea-pig, after having been perfused for a long time to wash out all the blood, is still susceptible to the sensitizing serum. A minute trace of the serum causes a well-marked uterine contraction. Similarly, the latent period in passive anaphylaxis is said to be due to the time taken to penetrate into the actual tissue cells. There is, therefore, no reason why anaphylatoxin should not be formed inside the cells as well as in the general circulation. As we shall see later, the assumption that the phenomena of anaphylaxis are due to an albumin-antialbumin reaction is very probable. An anaphylactic reaction is, therefore, in the true sense of the word, an immunity reaction, as was first insisted on by Wolff-Eisner, who even goes so far as to state that the fundamental law of immunity is hypersensitivity, not insensitivity.

Richet, who first propounded the idea of an albumin-antialbumin reaction in anaphylaxis, called the toxin resulting from the interaction *apotoxine*, the antibody *toxogénine*, and the antigen *toxine*. Von Pirquet believed that a special anaphylactic antibody is produced in addition to the usual antibodies (agglutinins, lysins, &c.).

A larger number of writers, however, are inclined to identify the anaphy-

lactic reaction with the known specific antibodies, precipitins (Friedberger), lysins (Nicolle and Wolff-Eisner), complement fixors, &c. Friedberger showed that when the serum of a guinea-pig which has received an injection of horse serum was mixed with horse serum in a test-tube, a precipitate was formed, and that this precipitate, if collected and treated with fresh guinea-pig serum, when injected into guinea-pigs caused anaphylactic symptoms. He therefore concluded that anaphylaxis was analogous to the precipitate reaction, the toxic element consisting of three constituents, antigen (foreign serum), precipitin (antibody), and complement (fresh guinea-pig serum). This toxic substance in the mixture he termed 'anaphylatoxin'.

The fact that complement is found to disappear in the above experiment and also from the blood of a guinea-pig after it has shown symptoms of an anaphylactic shock was held to support his view, as did also Scott's observations, that there was a distinct relation between the degree of hypersensitiveness in a rabbit and the amount of precipitin present in its serum. Friedberger carried his analogy further and suggested that an anaphylactic reaction might be similar to the fixation of the complement reaction. He found that any means by which the fixation of the complement was prevented also hindered or prevented an anaphylactic shock, such as by hypertonic salt solution.

More recent work, however, casts considerable doubt on Friedberger's hypothesis, as (1) it has been found that the precipitate is toxic without the addition of complement (Doerr); (2) in a certain number of guinea-pigs after an anaphylactic shock no loss of complement can be demonstrated; (3) while the analogy between precipitins in the rabbit and degree of sensitization proves nothing, as in that animal the technique of sensitization and preparation of precipitins is identical; (4) a serum may have strong hypersensitizing power for passive anaphylaxis and yet have no precipitating power (Doerr and Russ); (5) Biedl and Kraus say Friedberger's anaphylatoxin does not produce on injection the classical symptoms of anaphylaxis.

Bordet has likened the reaction to an absorption phenomena, the interaction absorbing some constituent of the serum, leaving the residue toxic. In support of this view he demonstrated that guinea serum (fresh normal), if absorbed by agar, when injected into a normal guinea-pig produces anaphylactic intoxication. A similar effect is said to be produced by filtration (porcelain filter) of fresh guinea-pig serum.

In 1907 de Waele showed that intravenous injections of peptone induced phenomena apparently identical with those observed in anaphylactic reactions in the dog or guinea-pig. More recently it has been found that simpler proteid derivatives, such as B. imidazoethylamine (histamin), can produce the same results. Biedl and Kraus, after a series of experiments, came to the conclusion that the anaphylactic symptoms in the guinea-pig and dog were identical with those of peptone poisoning. They believe that an injection of foreign proteid leads to the formation of a prosubstance which unites with any free proteid and forms a degradation product, allied to or contained in peptone. To the

active substance they gave the name vasodilatin, as its main action is to dilate the peripheral blood-vessels.

There is also some evidence to show that the anaphylactic poison is at any rate allied to peptone, as such a substance is found to be present in a mixture of the serum of a sensitized animal and the injected proteid (Biuret reaction). This body resists heat at 53°C. but is destroyed at 65°C.

The pendulum, however, has swung round against this simple explanation of the reaction. It has been shown that in a guinea-pig a previous anaphylactic shock does not protect against the toxic effects of an injection of peptone, neither does an injection of peptone protect a sensitized animal against an anaphylactic shock. Moreover, one can vaccinate an animal against anaphylaxis by subcutaneous injections of the antigen, but protection against peptone poisoning can only be obtained by intravenous injections (Besredka).

The error, of course, has been in seeking such a simple explanation of anaphylaxis without taking into account the probable presence of related proteid derivatives and intracellular reactions.

#### *Anaphylaxis in Medicine.*

As previously mentioned, there appears during the course of certain acute infections certain phenomena which are now considered to be anaphylactic in nature. An anaphylactic reaction, as pointed out, is an immunity reaction, so that these phenomena are to be looked upon as resulting from a protective reaction of the tissues against the invading microbe.

Von Pirquet, who was the first to indicate the nature of these reactions, also gave an elaborate explanation of the various phenomena. Primarily they owe their origin to an interaction of an antigen (microbe or some foreign proteid) and its antibody, the degree and rapidity of the reaction depending on how long the antigen has acted on the organism.

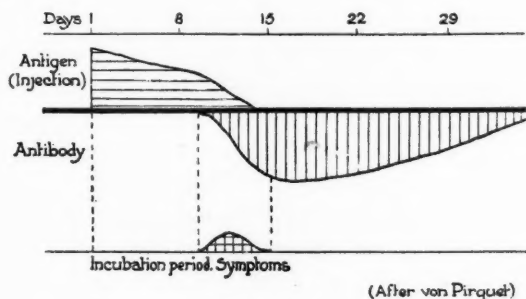


FIG. 1.

In the normal reaction, as it were, the antigen, after circulating in the system for some days, is suddenly confronted with the antibodies (both humeral

and intracellular) which the system has elaborated, and endotoxins are liberated to react on the tissue cells, which were gradually being sensitized to the toxins in the prodromal stage. In this way the rashes of most of the acute infections and those after serum injections are produced. The above diagram of von Pirquet shows what happens in the case of serum disease.

But von Pirquet showed that considerable variation could occur, especially after second injections of serum or in second attacks, these being due to antibodies which remain over in the system, or to the body cells having acquired the power to elaborate antibodies much more rapidly.

Von Pirquet described three types of altered reaction. (1) An alteration in the reaction time, as seen in the reaction which occurs immediately after the application of the foreign proteid—immediate or *sofortige* reaction—or, some time later, quickened or *beschleunigte* reaction. Either is an instance of an acceleration of the reaction time (Fig. 1 and Fig. 2).

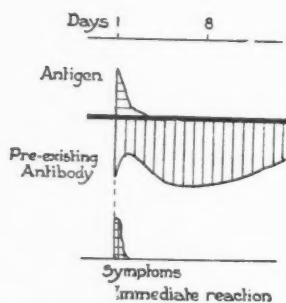


FIG. 2.

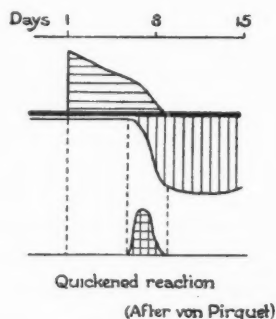


FIG. 3.

(2) Quantitative change in the reaction, when increased anaphylaxis or hypersensitiveness; when diminished or absent—insusceptibility, anergie, or immunity. Thus changes may be observed in the local reaction of tuberculous patients to tuberculin, and in the case of revaccination with calf lymph.

(3) Qualitative change in the character of the cellular reaction.

#### *Serum Disease.*

In some 10 per cent. of patients injected with antitoxic or other foreign sera symptoms of intoxication appear in seven to twelve days after the injection. Usually these consist of a rash of an erythematous or urticarial nature, with constitutional symptoms, fever, &c. If the case is at all severe there is oedema of the face, pain in the joints, and albuminuria. The inoculation site may be red and oedematous with swelling of the neighbouring lymph-glands.

The above state of affairs, however, is much more likely to happen after a reinjection of the serum, in fact it is to be expected in 90 per cent. of reinjections. The symptoms are as a rule more severe, and may even be alarming; they come on either immediately after the injection or some days later (five or six days). In the worst cases the signs of intoxication appear immediately, there being great distress, dyspnoea, collapse, and even convulsions and death.

The interval of time between the giving of the reinjection and the appearance of the symptoms depends mainly on the interval between the first and second application of the serum. If the period is over six months then the late reaction is to be expected, and if under six months the immediate.

Much can be done to prevent the occurrence of serum disease by the choice of a brand of antitoxic sera prepared from specially selected horses. The sera of certain horses seem to possess abnormal toxic properties, and by weeding out all such horses a less toxic brand is obtained. If there is some doubt as to a patient having had a previous injection of horse serum, a very small dose may be injected subcutaneously, and if no local reaction follows immediately it is very improbable that any severe reaction will follow a large injection of serum. Besides, the small injection has the power of desensitizing the patient. If possible, a second injection of serum should be given before the tenth day, that is, in the incubation period; this, as already stated, desensitizes the patient. More recently a better way out of the difficulty has been demonstrated, and that is to employ antitoxic sera made from different animals. If the first injection consisted of horse antitoxin serum, reinjections might be made of ox antitoxic sera. Such sera are already on the market.

#### *Vaccination and Revaccination.*

Vaccination, one of the world's greatest benefits, undoubtedly owes its origin to Jenner's faith and persistence in applying the neglected traditions of dairymaids. In the altered reaction of revaccination we have one of the oldest observed manifestations of Allergie. Jenner himself observed that vaccination on individuals who had previously suffered from an attack of small-pox did not produce the typical vaccine disease. The resulting lesions, if any, were smaller and were without the characteristic surrounding blush.

The inoculation of calf lymph into the skin of an unvaccinated person gives rise to a series of definite symptoms. For the first two or three days after the application of the virus only a slight local redness is seen (traumatic reaction). About the third or fourth day a faint redness appears round the inoculation area, the area of redness gradually enlarges, and coincident with this a papule gradually forms. The papule increases in size peripherally, and about the fifth day it becomes a vesicle. By the eighth day it has reached its fullest development, showing the characteristic depression at its centre. The areola increases in size



and brightness till the ninth or tenth day, about which time constitutional symptoms appear. About the eleventh or twelfth day the whole process commences to subside.

In revaccination either no lesion, a slight one, or more rarely a severe lesion, follows the application of calf lymph, depending on the degree of susceptibility present. In an individual who has been vaccinated only a short time previously the papule reaches its full development in twenty-four hours (instead of ten days), and by the second day has commenced to decline. The areola is distinct within twenty-four hours, but is small in size. Revaccination on an individual who has been vaccinated many years previously usually results in what might be termed a genuine 'take', though the course of the disease is considerably shortened. In revaccination the hypersensitiveness of the patient results in the rapid production of a papule and areola.

An interesting feature brought out by von Pirquet was that if a series of vaccinations be performed at intervals of one day on an unvaccinated person, the maximum development of the areola in each lesion occurred at the same time (i. e. tenth day after first application of the lymph).

#### *Tuberculosis.*

The application of Koch's tuberculin as a remedy for human tuberculosis led to the discovery of the hypersensitiveness of tuberculous patients to tuberculin, and to the application of tuberculin for the diagnosis of human tuberculosis, the first use of an anaphylactic reaction as a diagnostic measure.

*General tuberculin reaction.* So sensitive is the system of a tuberculosis patient to tuberculin that a subcutaneous injection of as small a dose as 0.00001 c.c. is often sufficient to bring about the reaction. The main feature of the reaction is a rise of temperature from 2° to 3° F. six or eight hours after the injection, together with general malaise, headache, and loss of appetite. Occasionally the local symptoms of the disease become more pronounced; in phthisis increased expectoration with pain in the chest, in lupus the patches frequently become distinctly hyperaemic and swollen, while at the site of the subcutaneous injection there is occasionally a local oedema and swelling.

After repeated injections of small amounts of tuberculin the patient loses all susceptibility to tuberculin, in fact is desensitized. Theoretically one ought not to attempt to use large therapeutic doses of tuberculin until one has got rid of the great susceptibility which tuberculous patients show to tuberculin. Failure to bring this about, especially in this country, is no doubt one of the chief reasons why on the whole the results have been so poor. The method ought to be to get rid of the hypersusceptibility and then to immunize the patient with large doses.

*Local tuberculin reactions.*—At present Koch's general reaction has, on account of the severe general discomfort which may arise, been entirely replaced by what is termed the local tuberculin reactions, of which there are three.



Von Pirquet's cutaneous reaction consists of an intradermic application of tuberculin, usually by placing a drop of a 50 per cent. solution of tuberculin on the skin and scratching it in as one does when vaccinating with calf lymph. In a tubercular patient the characteristic lesion (formation of papule with local redness and oedema) appears from twenty-four to forty-eight hours; if later the reaction ought to be regarded with suspicion.

The Wolff-Eisner or Calmette conjunctival reaction consists of the instillation of a drop of a 1 per cent. dilution of tuberculin into the conjunctival sac. If the patient be tubercular the conjunctiva becomes red and swollen in from six to twelve hours. On account of a very severe conjunctivitis occasionally occurring this test has practically been given up.

Moro's percutaneous reaction consists of rubbing into a small area of skin an ointment composed of 60 per cent. of tuberculin; if tubercular a dermatitis follows.

The tuberculin reaction is on the whole specific in its action, and only occurs in tuberculosis and occasionally in closely allied conditions, such as leprosy and actinomycosis.

No theory has yet fully explained the tuberculin reaction, though it is now generally admitted to be of an anaphylactic nature. One of the chief objections to this view is the difficulty of sensitizing healthy animals to tuberculin by injections of tuberculin, a result no doubt due to tuberculin not being absolutely identical with the toxin produced *in vivo*. Tuberculin in itself possesses only slight toxic properties. It is interesting to note that the tuberculin lesion shows histologically a close similarity with a tubercle. Wolff-Eisner considers that the sera of tubercular patients contain a lysin for the tubercle bacillus, and in the process of lysis endotoxin is liberated, but at the same time this lysin has the power of liberating endotoxin from tuberculin. In time the tissues become sensitized to the endotoxin, so an injection of tuberculin causes a reaction as it leads to the formation of endotoxin. A patient repeatedly injected with tuberculin in time ceases to react, as his tissues have been desensitized, and not because he has been immunized. Wassermann and Bruck hold that an antibody (antituberculin) to tuberculin is present in the sera of tubercular patients, and that they have a great affinity for each other; the reaction following as the result of this union, the stimulation of local lesions being due to an excess of antituberculin locally in the tissues.

Closely related to the tuberculin reaction are the mallein reaction in glanders and Twort's reaction in Johnes's disease of cattle. (Chronic enteritis due to a lepra-like bacillus.)

### *Syphilis.*

In the production of the various manifestations of syphilis it seems highly probable that anaphylaxis plays a very important part. The presence of the spirochaetes in the tissue induce an increased susceptibility to their presence.

The type of lesion resulting depends on the degree to which the tissues have been sensitized. That a varying susceptibility of the tissues to the syphilitic virus exists has been demonstrated by the reinoculation of syphilis virus.

Reinoculation in the incubation or primary period is followed by the development of an atypical primary lesion. The lesion is usually smaller, has a shorter incubation period than the original sore, and contains numerous spirochaetes. Therefore, even in the primary or incubation period, the tissues have already been influenced by the syphilitic virus and react differently to a normal individual. In von Pirquet's terminology the tissues are under the influence of *Allergie*, and here the susceptibility is diminished. Reinoculations made in the later primary or in the secondary period do not produce any lesions, the patient being insusceptible. The individual in this stage is said to be in a state of *Anergie* or complete insusceptibility, a condition which persists during the whole of the secondary period. In the tertiary stage the tissues are hypersensitive and react to reinoculation by the formation of a nodule or ulcer.

This stage, however, differs from the primary stage in the fact that the *allergie* (sensitivity) is increased instead of diminished, so that a condition of hypersusceptibility exists. In the superinfection lesions of this stage no spirochaetes are to be found. Occasionally the lesion consists of an extensive ulcer, which is analogous to the ulcer occasionally produced in a tuberculous patient after an injection of tuberculin. Some authorities hold that these ulcerative lesions are as truly superinfectious as the lesions obtained in the primary stage, but the absence of spirochaetes, on their view, is difficult to explain away. Neisser holds that the tissues have been educated by the presence of spirochaetes to react to reinoculation in a way particular to the stage of the disease; this condition he terms '*Umstimmung*'.

*Allergie*, of course, is an immunity reaction, and in the actual production of the various lesions of syphilis the other immunity processes are at work as well. In the primary and secondary stage the decreased sensitivity is most likely due to an increased protective mechanism, the tissue cells together with the tissue fluids destroy the virus before it can take hold. It is unlikely, as some suggest, that the tissue cells fail to respond on account of their having grown accustomed to the presence of the virus. According to Levaditi, superinfections can only be obtained when the Wassermann reaction is negative. In trypanosome infections the appearance of the specific antibodies is practically coincident with the production of the Wassermann substances.

The secondary rash is brought about by the destruction of the spirochaetes in the skin. The appearance of the rash coincides with a sudden elaboration of fresh antibody, and the toxin liberated from the union of antibody and spirochaetes poisons the sensitized skin.

The spirochaetes in themselves do not appear to have any great toxic properties. In support of the above view the following two phenomena may be given.

Herxheimer's reaction (increase of, or first appearance of, rash after the

administration of mercury or salvarsan) is due to these chemotherapeutic remedies killing off the spirochaetes and liberating toxin. In the same way 'spirochaete fever', observed after an intravenous injection of salvarsan in acute syphilis, is brought about.

Malignant syphilis would be the expression of the syphilis toxin on an abnormally susceptible or highly sensitized individual.

It is in tertiary syphilis that sensitization reaches its maximum. The gumma is a true anaphylactic reaction, and the possibility of obtaining a hyper-sensitive skin reaction in this stage similar to von Pirquet's reaction in tuberculosis confirms the view. The Luetin test (Noguchi), as it is called, consists in the application of a killed culture of the *Spirochaeta pallida* to the skin. The injection is made intradermically with the aid of a very fine needle and a syringe. The reaction is fairly constant in manifest tertiary syphilis, and persistently negative in the secondary period.

In parasyphilis the author has reason to believe that the condition is also of an anaphylactic nature. The very extensive lesions without the presence of *Spirochaeta pallida* in any number must be due to the action of minute quantities of syphilis toxin on highly sensitized tissues.

The difference between the ordinary tertiary or gummatous lesion and the parasyphilitic lesion depends on the fact that in the former the reaction is in the lymph vascular tissues, while in the latter it is in some highly specialized tissue incapable of regeneration. The most striking example is perhaps the case of syphilis of the central nervous system. Thus cerebro-spinal syphilis is a gummatous reaction of the hypersensitive vessels and connective tissue parts which show proliferative changes, while parasyphilis, on the other hand, is the expression of a response of hypersensitized highly differentiated nerve elements which have no power of regeneration.

The recent experiments of Noguchi, where he could only produce general paralytic changes in the brains of rabbits by sensitizing with repeated injections of cultures of *Spirochaeta pallida* and then giving an intracerebral injection of syphilis virus, supports the above conception. In normal rabbits intracerebral injections of syphilis virus produces no alteration in the brain.

#### *Hay Fever.*

Hay fever is the term used to express that hypersensitive condition of the mucous membrane of the upper respiratory passages possessed by certain individuals to the pollen of plants, in particular certain kinds of grass. The attacks are usually limited to the spring or autumn. The symptoms consist of a redness and swelling of the conjunctiva and of nasal mucous membrane, profuse coryza, and nasal irritation. At times there may be severe asthmatic attacks. The redness and swelling of the conjunctiva can be produced in a susceptible

individual by the mere application of one drop of pollen extract to the conjunctiva. This procedure is used as a diagnostic test for the condition. The congestion of the conjunctiva proceeds with great rapidity after the instillation of the pollen extract; in fact, in as short a time as one minute there may be a well-marked redness.

Dunbar, who investigated the condition, considers that the pollen-grains contain a toxin. Wolff-Eisner says that this is not so, and the active agent is the pollen proteid itself. Dunbar has produced what he calls an antitoxic serum (pollantin) by injecting horses with pollen toxin, with which he claims to have obtained very good therapeutic results.

The results obtained, however, have not been quite satisfactory, and any alleviation of the condition obtained is believed to be due more to the mechanical protective properties of a serum on the mucosa than to any specific effects. More recently it has been claimed that the injection of vaccines, consisting of pollen-grains, has given better results (Freeman).

It is not unlikely, however, that there may be an abnormal absorption of pollen proteid by the mucous membrane, and this proteid is broken up by the normal lytic substance into a toxic body to which the tissues become sensitized. According to this view one can see how neither serum therapy nor vaccine therapy can have any great curative or preventive properties. Closely related to the above condition are those peculiar asthmatic attacks which are brought on by the presence of certain animals or plants.

#### *Urticaria.*

Many urticarias and similar conditions are undoubtedly an expression of hypersusceptibility towards certain foreign proteids. The intoxication may come from without or from within the body, and in this group may be classed the greater number of those peculiar manifestations known as idiosyncrasies.

Amongst urticarias from without may be mentioned those following the bites and stings of certain insects, nettle stings, and toxic primulas, though the most frequent cause is the ingestion of a particular foodstuff, the commonest of which are egg-albumin, milk, flesh of certain animals or fish (crayfish in particular), and certain fruits. Urticarias from within occur in pregnancy and in chronic constipation.

These instances of intoleration are explicable on the assumption of a constitutional hypersensitiveness. The individual so affected seems to possess an unstable vaso-motor system, as shown by an unabnormal irritability to certain stimuli. The lysin normally present liberates the toxin, for which there is an increased susceptibility. In the case of idiosyncrasy to foodstuffs, it is very likely that some fault, either of an anatomical or physiological nature, allows of the passage of unaltered proteid through the mucous membrane and a condition analogous to serum disease results.

The urticaria of drugs (bromide, iodide, antipyrin, and others) is more difficult to understand, and is quite different to the toxic effects of drugs from cumulative action. It has been suggested that the condition was due to the drug uniting with the body proteids and producing, as it were, a foreign proteid, to which the organism responded as to a serum injection. The demonstration of antipyrin in the fluid of the skin blisters of a susceptible patient and the possibility of the direct production of the lesion by the local application of the drug excludes the probability of any proteid combination.

#### *Eclampsia.*

Eclampsia must also be regarded as being of a constitutional nature, and the most likely cause of the condition is a reabsorption of the placental villi. The syncytium must be regarded as a heterologous proteid, and its presence must lead to the production of lytic antibodies. A further reabsorption of placental proteid results in an albumin-antialbumin reaction, with the production of the toxin (anaphylatoxin). The mother, in other words, is sensitized to the foetal part of the placental proteid. The vomiting of early pregnancy can be traced to the same cause. The pathological anatomical lesions of eclampsia show a marked similarity with those observed after the absorption of foreign proteids.

Quite recently it has been suggested that the phenomenon of birth is of an anaphylactic nature.

During the child-bearing period the mother gradually becomes sensitized to some product of the child, and at full term an excessive absorption of this substance leads to an anaphylactic contraction of the uterine muscle. Experimental evidence has, on the whole, not produced much in support of the theory, except in so far as an injection of foetal serum in a woman at full term seems to hasten the onset of labour.

#### *Hydatid Disease.*

If a hydatid cyst be accidentally opened during the operation for removal and some of the fluid allowed to escape into the body cavities, severe toxic symptoms arise at times which may even result in death. Evidently in such cases the individual is highly sensitized to the hydatid proteid.

#### *Rashes.*

In this group is included the majority of acute exanthematous infectious diseases (scarlet fever, measles, small-pox, &c.) the chief symptom complex of which are skin eruptions, and according to von Pirquet these are allergic in origin.

The virus during the incubation and prodromal periods stimulates the



production of antibodies and sensitizes the patient, while the prodromal symptoms are evidence of the effects of the toxin produced by the direct action of the virus. The outbreak of the rash and increased severity of the symptoms is caused by the sudden output of antibodies which acts on the virus and produces an excess of toxin on a sensitized system and so an exacerbation of the symptoms. The fact that the symptoms usually subside after the rash has fully developed must be regarded as proof that the virus has been overcome by the antibodies.

In many parts of the country this is quite a popular belief, as is instanced by the mother of a sickly child, which is known to have been exposed to infection but has as yet developed no rash, endeavouring by various procedures to stimulate the onset of a rash.

Anaphylaxis, even though it has merely been by analogy, has thrown considerable light on many abstruse clinical phenomena, and from a practical point of view this new insight into the processes of immunity indicate a more scientific and exact means of investigating, diagnosing, and treating such pathological conditions.

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## CRITICAL REVIEW: BACTERIAL ENDOCARDITIS

By IRVING SIMONS

### *Introduction and Historical Notes.*

THE history of bacterial endocarditis may be said to begin with Virchow (57), who in 1855 suggested the connexion between uterine infection and the vegetations found upon the heart valves in a post-mortem case.

Bacteria were, however, first demonstrated in the valvular vegetations by Heiberg in 1869 (58), and by the middle of the eighties ulcerative and verrucous lesions of the endocardium had been described. Klebs (59) and Köster (60) had found bacteria in both varieties of lesions, whereas Orth (61) could obtain them only from the ulcerative.

The organisms of bacterial endocarditis having been obtained from the heart valves with regularity, the experimental stage of investigation began in 1885 with Philopowicz (62) and Wyssokowitch (63), who were able to produce endocarditis in rabbits by the intravenous injection of pure cultures of these organisms. The latter investigator, however, was able to produce it with great regularity if he previously wounded the valves or endocardium of the animal by sounding the carotid artery.

Ribbert (64) had great success with intravenous injections of bacteria in potato emulsion without any preliminary endocardial traumatism, and produced right-sided lesions in this way. He was of the opinion that the bacteria worked their way into the valves after first involving the endocardium superficially. He considered the possibility of the embolism of the small vessels of the valves which had previously been suggested by Köster, but regarded this as a rarer form of pathogenesis.

Beginning in 1887, a series of reports by Weichselbaum (66), Fraenkel and Sängner (65), and ending with Harbitz (4) in 1899, classified the various types of organisms (streptococcus, staphylococcus, gonococcus, &c.) which were the causative factors for so-called malignant or septic endocarditis, and which were to be found readily post mortem in the blood and heart valves.

By this time it had become a well-known fact that bacterial endocarditis

might be considered to be of two varieties pathogenetically—the endocarditis was primary, or as Leube (67) termed it in 1890, a form of cryptogenetic septico-pyæmia with localization upon the heart valves; in such cases the organisms had entered the circulation through some portal of entry (tonsils, &c.) which was not clear to either the clinician or the pathologist, and having incited a lesion of the endocardium, produced a transient, or more or less constant bacteraemia from this central point; or the endocarditis was secondary, being only part of a general septicaemia, the organisms continuing to enter the blood-stream from one or more foci other than the endocardium.

Such conceptions of the pathogenesis of endocarditis and bacteraemia could never have been brought forth or verified without a study of the bacteriology of the blood-stream during life, and while this had been done sporadically by various observers at and previous to this time, yet modern blood-culture methods may be said to date from Sittmann (68) in 1894, who popularized the method of drawing blood aseptically from the large superficial veins and distributing it immediately into various fluid and solid media. Following him reports began to accumulate from Kraus 1895 (71), Grawitz 1900 (69), Kühnau (70), Lenhartz 1901 (3), and Canon 1903 (38), which placed the study of the bacteriology of the blood in endocarditis upon a firm basis. The two last observers may be said to have contributed and assembled more material, to have placed the subject upon a more logical basis, than any of the previous observers, and to have given the stimulus to the work of the last decade.

By the time their work had been contributed it was a definitely settled matter that primary bacterial endocarditis was to be considered as divisible into two groups. The first group was of acute onset, short duration (days, weeks, or at most a couple of months), and was known as acute bacterial endocarditis. The second group was of insidious onset and long duration (months, or even one to two years), and was known as chronic bacterial endocarditis. As will be seen later when the pathology is considered, there is essentially no difference in the general symptom-complex. Both have underlying them the central lesion of the diseased endocardium (usually valvular) and a consequent distribution of various embolic or metabolic lesions throughout the body, giving the disease its protean nature and allowing it to masquerade under various guises according as involvement of one or another organ overshadows the picture.

There seems to be, however, in general one point of difference besides the duration, and this is apparently the underlying factor in the determination of the shorter or longer duration. This duration in the case of a systemic disease like bacterial endocarditis is determined by the length of time that the defences of the organism and its vitality are able to withstand the toxæmia, i.e. provided that the patient does not succumb to some accidental feature (e.g. apoplexy). Now this matter of resistance seems to be largely dependent upon the variety of the infecting organism, for as a rule in the cases in which the organism is pyogenic and the peripheral lesions consequently purulent the course is apt to be shorter and the variety more acute, whereas, in those cases in which the organism in

question does not produce pus the course is more apt to be longer and the variety more chronic.

This leads us to the controversy which was rampant in the early years of the twentieth century as to what really constituted malignant endocarditis. The controversy was entirely over the question whether malignant endocarditis was septic endocarditis.

In this controversy Litten and his followers claimed that all septic cases were malignant, and that cases, in order to be classified as septic, must have ulcerations of the endocardium and resultant purulent metastatic foci. Litten (1, 27), in fact, in a report before the German Medical Congress in 1900, presented a splendid account of what he termed malignant non-septic endocarditis. In these cases the metastatic foci did not conform to the septic type (i.e. were not purulent). Lenhartz and his pupils (Schottmüller and others) stoutly claimed that pus production was not the key-note of the situation, and that they had studied cases similar to Litten's and had found that they were true malignant endocarditis, although notably of the proliferative rather than the ulcerative type; that they were associated with similar types of lesions in analogous situations and organs, were usually chronic and practically uniformly fatal, and were nearly all due to a certain variety of organism, a streptococcus, which they called 'mitis' because of its low virulence and 'viridans' because of its power of producing a green colouration upon blood-agar, rather than the haemolysis seen usually in virulent streptococci of the ordinary type.

Now although it may seem academic, such a discussion has been of value, and it would seem that the view most tenable at the present stage of our knowledge could be conservatively stated as follows:—

That malignant is an unfortunate term, inasmuch as we know now that not all cases of so-called malignant endocarditis are fatal, or that not all die directly of the endocarditis and the concomitant toxæmia. Healed cases have been described and will be discussed under this heading later.

That the term septic is unfortunate because many cases which conform to every other criterion are not associated with pus formation usually because the type of organism is not pyogenic, or more rarely because the particular strain of pyogenic organism has either partly lost its virulence or is of low chemotactic power in the particular case of the disease under discussion.

That the term ulcerative is unfortunate because many of the cases are associated with anything but ulcerations of the valves; in fact, the lesions of some forms are particularly proliferative or vegetative.

That the term infectious endocarditis is vague because it covers too many conditions and would embrace, e.g., syphilitic lesions or rheumatic lesions.

Eliminating the above defects, it would seem advisable to apply the term bacterial endocarditis to those cases in question which are either acute or chronic, are associated with the presence of bacteria in the valvular lesions and in the circulating blood during life for some (usually a considerable) period of time, and are usually of fatal outcome.

I have purposely designated that the organisms be found in the blood 'during life', and in doubtful cases it would be advisable that the findings of the last forty-eight hours be carefully scrutinized on account of the liability of agonal or prelethal invasions of the blood-stream of organisms which have played no part in the previous clinical picture but have entered the blood-stream prelethally (from the throat, gastro-intestinal, pulmonary, or urinary tracts) when the defences of the patient became lowered.

With our present accurate methods of blood-culture such demands can be made. One exception must be made, however, in the case of healing and healed cases of bacterial endocarditis, in which cases the blood is bacteria-free, and this will be dealt with later.

Such a criterion (i.e. the presence of living organisms in the circulating blood during life) would of course eliminate the cases of rheumatic fever which have been extensively studied.

Lenhartz, Canon,<sup>1</sup> and many other observers are particular to stress the fact that they found no bacteria in the circulating blood of patients with acute rheumatism and acute rheumatic endocarditis, and their stand is, I believe, the correct one. Conversely, they reason that no case with positive blood-culture during life can be rheumatism.

At this point it is necessary to digress slightly in regard to the bacteriological investigations regarding the aetiology of rheumatic fever made by certain investigators.

Beginning in 1892, investigations were published from time to time by Fraenkel, Sahli, Lanz, and others, and ending with Poynton and Paine in 1900, in regard to various infecting organisms obtained chiefly from rheumatic (or choreic) cases with which the observers were able to reproduce joint lesions in rabbits and other animals which clinically resembled rheumatic fever more or less. The literature is quite large, and will be found in the bibliography (in nos. 36 and 72 to 98 inclusive). It will suffice to say that most of them found streptococci and some pigment-forming staphylococci. Certain Frenchmen, particularly Achalme (1891), Thiroloix and Triboulet, found an anaerobic bacillus resembling anthrax, with which they claim to have reproduced the lesions experimentally.

<sup>1</sup> Canon was not able to find any organisms by culture or by microscopic examination of the blood of acute rheumatic fever, but occasionally obtained delicate streptococci some time after the acute symptoms had subsided. He is of the opinion that the streptococci found in rheumatic fever are only the inciting agents of a secondary infection, just as one finds them in cases of diphtheria, scarlatina, measles, and plague. The careful consideration of the case upon which Canon lays particular stress (p. 53, l. 32 ff., edition 1905) would lead one to believe that this case was one of the chronic streptococcus endocarditis which were so thoroughly described by Lenhartz and Libman.

However, this standpoint is of interest inasmuch as previous to Rosenow's work it seemed that the pathological lesions found (viz. an old sclerotic lesion with a new proliferative friable lesion on top of it) bore out the idea of a primary infection by a rheumatic organism (unknown) and a secondary infection by a second organism (usually streptococcus viridans).

In 1899 Wassermann, Westphal, and Malkoff isolated a very delicate coccus from the minute mitral vegetations of an acute fatal choreic rheumatism and produced fever and multiple arthritis in a series of eighty rabbits.

The above investigations were practically all based on post-mortem bacteriology and it is hence difficult to fix their status. Most of them, however, particularly the Achalme bacillus, have not stood the test of time. The last investigators in this list are Poynton and Paine. The organisms found were a form of attenuated streptococcus; they were recovered from five cases post mortem—from two from the blood ante mortem and from one from the tonsil ante mortem. Their organism seems to be similar to the Wassermann organism above mentioned, but I cannot understand how it can be classified as it is said by them to be easily decolourized by Gram's method. One point of interest and importance which they noted in the experimental heart lesions produced was that the valves were attacked from within, a point which will be brought out more fully when the recent investigations of Rosenow are discussed.

It is rather difficult to discuss these investigations and give them a correct status. Three years ago I should have been willing to discard them on account of the regularity with which I had been accustomed to see negative blood-cultures in rheumatism and rheumatic endocarditis. However, in the light of the investigations of Rosenow which will be discussed fully in summing up, I would be inclined to think that these observers were dealing with a group of cases which lay midway between the ordinary acute rheumatic endocarditis and the ordinary type of chronic bacterial endocarditis, or what Lenhartz has termed the malignant type of rheumatic endocarditis (although in the one case which he saw he was able to recover no inciting agent).

#### *Varieties of Endocarditis.*

In order more effectively to clear the ground for a discussion of bacterial endocarditis, it is advisable to determine its place in the classification of the various clinical types of endocarditis.

The following table, modified and enlarged from Litten's presentation before the German Congress for Internal Medicine in 1900, will show at a glance the various types of endocarditis considered from a clinical as well as an aetiological standpoint.

TABLE I.

Classification of endocarditis—modified from Litten (27).

I. Rheumatic endocarditis.

1. The usual benign form, including the benign choreic and benign gonorrhoeal (Litten (27), Romberg (28)).

2. The malignant rheumatic form (including malignant choreic form), (Poynton and Paine (36)).

II. Endocarditis of cachexia.

Occurring in cases of Bright's disease, carcinoma, tuberculosis, chronic cystitis, old nerve lesions (Simmonds (31)). They are considered as morant thromboses (Bartel (26)).

They are mere autopsy findings having no clinical significance.

III. Arterio-sclerotic endocarditis.

IV. Bacterial endocarditis, due to :

1. Ordinary streptococci.

*Streptococcus viridans* of Schottmüller (34).

*Endocarditis cocci* of Libman (18).

2. Small streptococci

Modified pneumococci of Rosenow (35).

Saprophytic streptococci of Horder (9).

*Streptococcus tenuans* of Hastings.

3. *Staphylococcus albus* and *aureus*.

4. Pneumococci.

5. Gonococci.

6. *Meningococcus*—Cecil and Soper (37).

7. *Bacillus coli*.

8. *Bacillus influenzae*.

9. *Bacillus pyocyaneus*—Canon (38).

The table is self-explanatory, and it is easily seen that by changing the term septic endocarditis (of Litten's original table) to bacterial endocarditis the more modern conception is satisfied.

*Aetiology of Bacterial Endocarditis.*

In the introductory section the criterion has been enunciated that in order that bacterial endocarditis be thoroughly and scientifically proven during life the organisms must be demonstrated in the blood-stream in cases in which the clinical symptoms allow the disease to be diagnosed tentatively; and not only that, but they must be demonstrated at a time sufficiently precedent to the patient's exitus so that the question of prelethal invasion will not enter in.

The following table (II) gives an analysis of 325 cases of endocarditis in which organisms were demonstrated in the blood by some of the more important observers in both acute and chronic cases.



TABLE II.  
Bacteriological Studies of Blood in 325 cases of Acute and Chronic Bacterial Endocarditis.

Strept.	Str. vir.	Pneumoc.	Staph.	Gonoc.	Men- ing- occi.	Unclasi- fied or- ganisms.	Bac. infl.	Colon.	Bac. Pyoc.	B. aerog. caps.	Mixed cultures Strept. and Staph.	Neg.
Harbitz (4) P.M. chronic *	9	4	—	3	—	—	—	—	—	—	—	16
Harbitz P.M. acute	8	1	8	—	—	—	—	—	—	—	—	27
Horder (9) A.M.	26	4	albus 1	2	—	1	6	—	—	—	—	40
Horder P.M.	62	19	aureus 7	3	—	1	5	1	—	1	1	100
Lenhartz (3) A.M.	3	3	albus 1	—	—	—	—	—	—	—	—	16
Lenhartz P.M.	2	3	aureus 4	1	—	—	—	—	—	—	—	9
Osler (6) A.M. chronic	2	—	aureus 1	—	—	—	—	—	—	—	—	10
Billings (5) A.M. acute	2	—	1	1	—	—	—	—	—	—	—	4
Billings A.M. chronic	3	—	—	—	—	—	—	—	—	—	—	14
Libman (18) A.M. chronic	—	—	—	—	—	—	4	—	—	—	—	75
Jochmann (24) A.M. chronic	—	—	—	—	—	—	—	—	—	—	—	7
Schottmüller (25) A.M. chronic	—	—	—	—	—	—	—	—	—	—	—	5
Cecil and Soper (37) A.M.	—	—	—	—	1	—	—	—	—	—	—	1
Blum (43) A.M.	—	—	—	—	—	—	—	—	1	—	—	1
												325

\* In some of these ante-mortem (A.M.) as well as post-mortem (P.M.) results are recorded merely for comparison. In one case (Harbitz) only P.M. results are recorded, as his work was entirely based upon autopsy findings and his discussion of the pathology is the first extensive work of importance upon the subject. The words *acute* and *chronic* will be seen in those cases where the authors separated their cases. In some cases (notably Horder and Lenhartz) the cases are grouped and hence these words are omitted. The numbers beside the authors' names designate literature.

† Billings calls these pneumococci.

Aside from the tabulation of the large number of inciting agents, the only point of real significance that can be learned from this table is, that of ninety-six cases of chronic bacterial endocarditis, ninety-two were caused by the streptococcus viridans and four by the bacillus influenzae.

We have included in this eleven cases of Billings, although he calls the inciting agent modified pneumococcus—we will use the term streptococcus viridans throughout this paper; it is now well understood that the organism which usually causes chronic bacterial endocarditis has been variously named by many observers (see Table I for five names by Hastings, Schottmüller, Libman, Rosenow, and Horder), but that these organisms are identical.

### *Clinical Aetiology.*

TABLE III.

Lenhartz—Acute and Chronic (10) (3).

Puerperium . . . . .	5
Angina . . . . .	2
Wounds of skin	
Ulcer of finger	
Gonorrhoea . . . . .	4
Urethral injury (bougies 7 cases) . . . . .	7
Croupous pneumonia . . . . .	5
Cholecystitis—Pneumococcus (2 cases) with pylephlebitis . . . . .	2
	—
	25 traced of 38 cases.

Billings—Chronic (5) . . . . . 14 cases

Pneumonia . . . . .	1
Tonsillitis . . . . .	2
Alveolar abscess . . . . .	2
Grippe . . . . .	1
Unknown . . . . .	8
Other aetiology suggested—abscess of aural cavity, infections of post-nasal antra, &c.	

Horder—Acute and chronic. Cases 150 (9).

Acute and subacute rheumatism or chorea . . . . .	72
Scarlatina . . . . .	10
Gonorrhoea . . . . .	7
Typhoid . . . . .	4
Malaria . . . . .	4
Syphilis . . . . .	2
Influenza . . . . .	2
Graves' disease, dysentery, pneumonia (1 each) . . . . .	3
No traceable aetiological factor . . . . .	46

These tables show several points of importance in the analysis of the clinical conditions which must be considered as forerunners of 202 cases of bacterial endocarditis.

Lenhartz rightly lays greater stress than his figures show upon the importance of the puerperium and pneumonia as well as lesions of the genito-urinary tract. In the latter cases urethral injury (instrumentation) either in the presence or absence of an acute gonorrhoea was an important factor. The bacteria

invading the blood-stream were not always gonococci, but in some cases streptococci and staphylococci, and in many a right-sided endocarditis ensued, suggesting a direct transference by a venous route to the right heart.

In Horder's cases the greatest stress is laid upon previous rheumatic manifestations, and hearts in the dead-house in subacute and chronic cases nearly always show signs of old endocarditis, which we are accustomed to recognize as rheumatic with the more recent bacterial lesions engrafted upon them.

Billings has laid considerable stress upon infection of the teeth, gums, ears, post-nasal spaces, antra, &c. Two of his cases followed alveolar abscess, but how important this factor is in general requires further study and reports.

### *Bacteriology.*

On referring to Table II a large variety of bacteria are mentioned as causative agents in bacterial endocarditis.

Analysis of these shows the following :—

In the acute forms are found :

Streptococcus pyogenes (common).	Gonococcus (fairly common).
Streptococcus viridans (very rare).	Meningococcus.
Pneumococcus (fairly common).	Bacillus coli.
Staphylococcus albus.	Bacillus pyocyaneus.
Staphylococcus aureus (common).	Bacillus aerogenes capsulatus.

In the chronic forms are found :

Streptococcus pyogenes (rare).
Streptococcus viridans (very common).
Pneumococcus (rare).
Gonococcus (very rare).
Bacillus influenzae (not common, but never found except in chronic cases).

This shows that the Gram-positive chain cocci occupy the important place among the bacteria which cause bacterial endocarditis.

On account of this it is of the utmost importance that their characters be thoroughly understood. The following Table IV will give the salient features of their differential characters.

TABLE IV.

Gram-positive Chain Cocci.				
	Pneumococcus.	Streptococcus pyogenes.	Str. mucosus caps.	Str. mitis seu viridans.
MORPHOLOGY—				
Capsule	Diagnostic	Non-diagnostic or absent	Diagnostic	Absent
Spreads	Lanceolate diplococci or chains	Usually round and may be very long chains	Similar to pyogenes	Str. Usually very small—round—may be chains of 10 or 12. Occasional diplococcal lanceolate delicate forms or bacillary
Gram	+	+	+	+
CULTURAL—				
Serum agar	Delicate, slightly mucoid; often 1-2 millimetres and characteristically ring-shaped	Very delicate and dry	Large mucus-like drops, 1-4 millimetres, dry rapidly	Very delicate, dry, hard to scrape off
Serum glucose agar	No precipitation (rarely +)	Precipitation	No precipitation (rarely +)	Precipitation
Bouillon	General turbidity	Tendency to fall to bottom or on lower slanting surface of tube in sawdust-like formation	General turbidity	Delicate lace-like formation which falls to bottom
Plain agar-blood plate	Colonies develop in 24 hours; 1 millimetre, lenticular yellow with green ring—no haemolysis, except rarely in patient's own blood	Colonies develop in 24 hours; 1 millimetre, lenticular yellow, usually with haemolytic zone and rarely several with target-like formation; may be absent however	Colonies develop in 24 hours; 1-3 millimetres, lenticular yellow-green ring as a rule—no haemolysis. Surface colonies large, 4 millimetres, dew-drop with stippled granules	Colonies develop in 48-60 hours. Fine points or very delicate lenticular shapes, and at times square forms. Green ring very fine; on 3rd-4th day this may be clear. In glucose blood-agar the colonies show precipitation on 2nd-4th day
Inulin fermentations	Positive, but not in every generation	Negative, rarely positive	Positive	Positive Negative
Solution in bile	Positive	Negative	Positive	Negative

NOTE 1. For the capsule as a diagnostic criterion, see Buerger (102).

NOTE 2. By precipitation is meant the whitening of glucose serum-agar due to the production of acid by the growth of the organism and the subsequent coagulation of the protein in the serum (usually ascitic fluid). See Libman (98).

NOTE 3. The growth of the organisms upon and their differentiation by means of blood-agar plates was excellently recorded by Schottmüller (34).

Schottmüller's name, for the organism *Streptococcus mitis seu viridans*, which is the most common causative agent in chronic bacterial endocarditis is used throughout this paper as it is probably the best descriptive name. Billings and Rosenow call their organisms modified pneumococcus.

NOTE 4. For inulin studies; see Buerger (99 and 100).

NOTE 5. For studies on bile as a solvent of capsulate cocci, see Mandelbaum (101).

*Pathology of Bacterial Endocarditis.*

Bacterial endocarditis is a disease of the entire economy. It is in the old sense of the word a septicaemia, or as we prefer to call it a bacteraemia. Consequently in addition to the cardiac lesion present there are various peripheral manifestations due in part to embolic processes and in part to toxic and inflammatory causes.

Many of these manifestations will be best discussed under symptomatology, but under the present heading we will discuss the lesions of the heart, brain, and kidneys as they have been very well reported. It is advisable to distinguish the lesions of acute and chronic endocarditis.

*The Heart.*

The following table will show at a glance the valves usually affected. In the reports of these 171 post mortems there was no discrimination of acute or chronic forms.

TABLE V.

	Holder (9).	Billings (5).	Lenhartz (8).
Mitral . . . . .	38	7	18
Aortic . . . . .	22	1	11
Mitral and Aortic . . . . .	63	5	2
Tricuspid with mitral or aortic or both	14	—	—
Pulmonary with mitral or aortic or both	7	—	—
Auricular mural infection . . . . .	43	—	—
Ventricular mural infection . . . . .	8	—	—
Pulmonary . . . . .	—	1	2
Mitral and Tricuspid . . . . .	—	1	—
Tricuspid . . . . .	—	—	4
Aortic and Tricuspid . . . . .	—	—	2
Number of autopsies . . . . .	118	14	38

This table shows the preponderance of left-sided lesions of the valves either singly or in combination; in addition to this there are a striking number of mural infections of the auricle in Holder's case which, while not specified here, must refer to the left auricle, as will be substantiated by the table of Libman's cases to follow.

TABLE VI.

Autopsy records of hearts of 34 cases of chronic infective endocarditis (Libman (18)) showing position of lesions.

Auricle, mitral valve and chordae				17
Auricle, mitral valve, chordae and aortic valve				5
Auricle, mitral valve				2
Mitral valve, chordae				1
		Aortic valve		3
	Chordae, aortic valve, aortic flap of mitral			4
Mitral valve, chordae, aortic valve				1
Auricle, mitral valve, aortic valve				1
25	27	28	10	34

As a rule acute bacterial endocarditis is engrafted upon an uninjured valve, whereas in the chronic forms the bacteria commonly seek these areas of previous chronic rheumatic (?) inflammation and proceed to cause vegetative polypoid and proliferative lesions, in contradistinction to the usually ulcerative type seen more commonly in acute cases. This seems to be connected with the more destructive nature of the streptococcus pyogenes and staphylococcus in contradistinction to the streptococcus viridans and bacillus influenzae.

The pneumococcus seems to be somewhat of an exception in that it can form large globose vegetations in the short duration of an acute case. I have seen a case following puerperal infection in which vegetations as big as the terminal phalanx of the little finger were present at autopsy no more than a week after the criminal abortion. The gonococcus, too, seems to have some tendency in this direction, forming at times masses the size of a hazel-nut with softened centre which may contain a *Brei* showing the gonococci. One gonococcus case of only three weeks' standing (18) gave lesions like those of a streptococcus viridans case.

But to return to the actual lesion in the heart, right-sided lesions are more common in acute than in chronic forms; this is chiefly due to the pneumonic and urethral paths of infection. They occurred in 18 per cent. of Lenhart's cases, a considerable number of which were acute. Why the puerperal cases are not prone to cause right-sided lesions is not understood.

As mentioned before, even in acute cases, however, the left side is more commonly attacked, and a common lesion is an ulcerative condition with more or less destruction of a mitral or an aortic valve. In some cases there are abscesses in the heart muscle, especially in the staphylococcus aureus cases, the small yellow foci often approaching the surface and resulting in a purulent pericarditis, a common terminal event in these cases. As a rule the acute cases are so rapid that there is no sign of reparative or defensive process on the part of the valvular tissue.

In chronic endocarditis the lesions are quite typical. As a rule we find here (see Libman's table) considerable proliferative vegetation of the mitral valves. These vegetations are variously coloured—greyish, pinkish, and greenish; they are soft and friable; they extend upward, creeping over and involving often a good part of the left auricular endocardium; they extend downward along the mitral chordae tendineae, being here somewhat destructive and causing ulceration and often rupture of the chordae.

In the aortic valves the lesions are similar, but result often in aneurysms and ruptures of the valves, which processes are less common in the mitral valves.

As a rule there is marked evidence of previous inflammation, in other words, of a previous healing of a process that we have termed rheumatic endocarditis. It is now a debatable question as to whether these old lesions upon which the more recent endocarditis is unquestionably engrafted are really of a different nature aetiologically than the newer lesions that have caused the *dénouement* of the patient.



In other words, is there a rheumatic lesion followed by a bacterial lesion, or are they both bacterial lesions? Is the older lesion a healed type of a bacterial lesion to another attack of which the patient succumbed?

This is an extremely difficult matter to settle inasmuch as we have no definite aetiological factor for rheumatism. Nevertheless it would seem that we have presumptive evidence in favour of the latter idea along two lines—Libman's investigations of healed lesions of chronic bacterial endocarditis and Rosenow's animal experiments on chronic bacterial endocarditis.

It must be held in mind that chronic bacterial endocarditis is practically always caused by the streptococcus viridans, and rarely by the bacillus influenzae. Libman (18) found the former in sixty-nine and the latter in four cases out of seventy-five cases reported. In two he obtained negative cultures after repeated efforts.

TABLE VII.

Analysis of Healed Endocarditis Cases (Libman (18)).

Clinical Diagnosis.	Kidneys.	Hearts.	Valve Section.	B. C.
I. Chronic nephritis, uraemia	Typical glomerular lesions	Typical	No bacteria	Negative
II. Chronic nephritis, uraemia, chronic endocarditis	"	"	"	" (1)
III. Chronic endocarditis, anaemia, femoral aneurysm	"	"	Few poorly staining cocci	" (3)
IV. Chronic endocarditis, chronic nephritis	"	"	No bacteria	—
V. Chronic endocarditis with fever	"	" (calc.)	"	Negative (2)
VI. Chronic endocarditis with fever. Embolic aneurysms of iliac artery	"	"	"	" (3)
VII. Chronic endocarditis with fever. Cerebral embolism	"	" (calc.)	"	" (3)
VIII. Subacute bacterial endocarditis in bacteria-free stage	—	"	"	" (1)
IX. Subacute bacterial endocarditis. Bacteria-free stage. Cerebral embolism	Typical glomerular lesions	"	"	" (3)
X. Subacute bacterial endocarditis. Bacteria-free stage. Brachial aneurysm	"	"	"	" (2)
XI. Chronic endocarditis, anaemia, exhaustion, decompensation	"	"	"	" (9)

NOTE.—The numbers in brackets in the B. C. column signify the number of blood-cultures made during life.

Carefully studied autopsies of these cases and others that followed merits the following:—

1. That some cases of chronic bacterial endocarditis die without the bacteria being demonstrable in the blood-stream by our present methods.

2. That such cases show typical lesions (aortic, mitral, auricular, and chordal) of chronic bacterial endocarditis.

3. That in these cases the valvular lesions are firmer, less friable, and show no signs of organization or healing; in most of them sections do not show any bacteria or only a few poorly staining cocci.

4. That there are diagnostic glomerular lesions in the kidneys of chronic bacterial endocarditis. (See Pathology of the Kidney.)

5. That many of the cases which escape sudden death from embolism or more or less rapid death from toxæmia go on to temporary recovery, becoming bacteria-free, but subsequently die of cardiac decompensation or uræmia.

6. That many cardio-nephritics post mortem show lesions in the heart which resemble chronic bacterial endocarditis in their position and seem to be healed lesions of a former chronic bacterial endocarditis.

Rosenow in a masterly series of experimental works has cleared the way for an intelligent consideration. He came to the conclusion (41) in the first place that the organisms variously designated by Schottmüller as *streptococcus mitis seu viridans*, by Horder as saprophytic streptococci, by Hastings as *streptococcus tenuans*, by Libman as endocarditis cocci, and by himself as modified pneumococci are essentially the same organism, although he contends for various very logical reasons that his organisms are biologically nearer to pneumococci than to streptococci.

Experimenting with rabbits he found that he could easily produce endocarditis by injecting these modified pneumococci. He injected them subcutaneously, intravenously, and intraperitoneally, often combining the several methods. In none of his cases, however, did he produce lesions of the endocardium by merely intraperitoneal injection (35). Intravenous injection was the most efficacious. The organism would produce endocarditis only as long as it retained the clumped formation which is so characteristic of it when grown in bouillon or agar; this clumped formation could be made to disappear by cultivation (especially under anaerobic conditions) and by animal passage, the latter, however, not interfering with its virulence, the animals, in fact, dying more rapidly of a pneumococcaemia, ordinary pneumococci being recovered; in other words, the organism had undergone mutation in the animal body.

The modified pneumococci are of low virulence; very large doses, however, will kill a rabbit in twenty-four hours. In such an animal haemorrhages were found in the valves and in the papillary muscles. The organisms could not be recovered from cultures of the endothelial surfaces over the haemorrhages, but were readily recoverable from the haemorrhage itself. From this one must conclude that the lesion is regularly an embolic one, contrary to the views of Köster (44) and Lissauer (45), who claim that this is a rare occurrence. The bacterial emboli, however, are not demonstrable in these areas before forty-eight hours. (This is also the average time for the appearance of the colonies on a blood-agar plate.)

In cases where sublethal doses were injected the animals would live days

or weeks, or even recover. This process was dependent upon the slow development of endocarditis at the sites of the former haemorrhages, and in some cases to the complete healing of the endocarditis.

The development of vegetations was noted as early as two days. The healing tendency seemed to be the rule, and was noted as early as seven days. Rosenow was able to show completely healed endocarditis (i.e. puckered valves without vegetations) as early as seventeen days when the organisms were previously killed by heating them to 60 degrees C. for one hour; proving at the same time that the mechanical or embolic idea of pathogenesis is correct. Absolutely healed lesions were demonstrated fifty days after inoculation with living cocci. Rosenow believes that the same organism can produce both the simple endocarditis and the fatal or malignant form when engrafted upon an old lesion.

In the former case the conditions of repair are better and the healing takes place before the ulceration. In other words, what we have been formerly calling rheumatic endocarditis are merely healed lesions caused by the same cocci that cause ulcerative or malignant endocarditis.

After vascularization of the valve occurs scar formation then results, and the valve then becomes relatively avascular, containing only fine capillaries. This predisposes to reinfection. In the sclerosed condition of the valve healing of subsequent infections by reparative process is more difficult and the malignant or fatal form ensues, the vegetative process getting the better of the valve.

'The fact that efforts at healing (sclerosis, calcification), even in the fatal cases in man, are often present, as pointed out by Libman, together with the fact that I have produced simple endocarditis and sclerosis of valves experimentally, with cocci from chronic forms of endocarditis, speaks in favour of the view that, contrary to what is assumed on clinical ground, the organisms which produce the fatal form of the disease may also produce different grades of simple or benign endocardial inflammation.' (Rosenow, *Jour. Inf. Dis.*, xi. 2, p. 222.)

To return again to the morbid anatomy of the heart, the rôle of congenital defects in the heart as a predisposing cause of endocarditis deserves mention, inasmuch as eight cases in Horder's 118 post mortems showed such lesions. The lesions noted were:

Two aortic cusps; two pulmonic cusps; open foramen ovale and other septal defects (here direct extension of vegetations from the left to the right side of the heart was seen); open ductus arteriosus (in one case this offered a point of beginning for vegetations which crept down the pulmonic artery as far as the opening of the pulmonic valves).

*Mycotic Aneurysms of the Heart Valves.*

These formations seem to occur only in the chronic form of bacterial endocarditis. They are not common in my experience, although Horder has reported them in twenty of his 118 post mortems. His list is as follows :—

Aortic . . . . .	7
Mitral . . . . .	5
Wall of heart . . . . .	4
Interventricular septum . . . . .	4

I have seen these formations most commonly in the aortic valves. They consist of cup-like formations in the vegetations of one or more cusps, the bottom of the cup pointing downward toward the heart chamber. Very often there is a perforation in the bottom and rupture of the valve may result. How many ruptures of valves in this disease are preceded by aneurysm is of course impossible to say.

*Embolie Aneurysms of the Vessels.*

These peculiar lesions deserve more than casual mention. They are, as their name states, aneurysmal dilatations of vessels which follow embolism. They are extremely rare in heart disease, but are not uncommon in chronic bacterial endocarditis. It has never been my good fortune to observe a case except in chronic bacterial endocarditis (of streptococcus viridans or B. influenzae origin). Libman has, however, reported a case in which he found staphylococcus aureus in the aneurysm and staphylococcus aureus and streptococcus in the circulating blood.

The aneurysms are due to one of two factors: either a large fragment of vegetation from a heart valve is carried suddenly and lodges in an artery; or there is an infection of the arterial wall (by way of the vasa vasorum) by bacteria of low virulence which are circulating in the blood. It is impossible to decide which is the method of pathogenesis; at any rate a thrombus is formed and finally an aneurysm results. Sections of the material in the sac are practically indistinguishable from sections of vegetations of the heart valves, being formed by fibrin, leucocytes, and bacteria. At times (7) the intima of the vessel is found continuous into the aneurysmal sac and there are often calcareous deposits in the sac.

Libman has divided embolic aneurysms into:

## 1. Non-mycotic embolic aneurysms.

In these cases he could not obtain positive cultures from the material removed from the sac. This distinction, it would seem, loses its importance in consideration of what we know of healing and healed endocarditic lesions.

## 2. Mycotic embolic aneurysms.

3. Aneurysms due to infection of the wall of the vessel by bacteria in the lumen.

The distribution of embolic aneurysms is of extreme importance. (See section on symptomatology and differential diagnosis.)

TABLE VIII.

## Distribution of Embolic Aneurysms.

Pial arteries . . . . .	Simmonds (31)
Arteria sylvia . . . . .	Lenhartz (10)
External carotid . . . . .	Horder (9)
Facial (?) . . . . .	Billings (5)
Aorta	
Arterio-venous aneurysm with vena iliaca dextra . . . . .	Lenhartz (10), p. 399
Coeliac axis	
Gastric . . . . .	Horder (9)
Splenic . . . . .	(own observation)
Right branch of hepatica . . . . .	Libman (8)
Superior mesenteric . . . . .	Libman (8)
Renal . . . . .	Libman (7)
Uterine . . . . .	(own observation)
Sciatic (?) . . . . .	Billings (5)
Radial . . . . .	(own observation)
Ulnar . . . . .	(own observation)
Femoral . . . . .	Libman (7), Schottmüller (25)
Popliteal . . . . .	Libman (8)

NOTE.—These cases are all that I have been able to find in the literature. Further bibliography is to be found under Nos. 46-54.

The aneurysmal sacs vary in size from a pea, as they occur in the brain, to a huge sac the size of a large orange, as they are at times seen in the femoral region. In the brain they often give rise to haemorrhage by their rupture. In the femoral and popliteal region they erode bone markedly. In the abdomen they are usually of very small size and are often multiple when found in the superior mesenteric arterial branches. They are at times arterio-venous.

*Pathology of the Kidney.*

The lesions in the kidney of bacterial endocarditis may be divided as follows: (1) single or multiple abscess (purulent infarcts); (2) bland infarcts; (3) embolic focal nephritis.

The infarct is the distinguishing feature of the pathology of the kidney of endocarditis. In the acute forms the lesions are practically always multiple, bilateral, and purulent. In the early stages of this formation the kidney is turgid, swollen, and congested. Its capsule strips easily and presents numerous small, raised, reddened areas about the size of a split pea. These areas on closer examination show a whitish centre which later breaks down into pus. On gross section the areas are wedge-like in shape, and usually extend into the kidney to a depth of about 5 mm. These infarcts are indistinguishable from those occurring in a general bacteraemia without endocarditis.

These areas may be found also in the depths of the renal parenchyma. The pus evacuated is either yellowish and creamy in the case of the staphylococcus aureus, or thin and serous in the case of the streptococcus pyogenes.

The rest of the kidney presents in addition the general lesions of an acute haemorrhagic nephritis. Microscopic sections show areas of acute inflammation with polynuclear infiltration and bacterial emboli. These kidneys are also indistinguishable from the kidneys of unilateral septic infarction (55, 56) except that they are nearly always bilateral.

Bland infarction of the kidney is quite a different matter. Such kidneys present on their surfaces numerous indented irregular areas, at times lentil-sized, and at times several centimetres in diameter. They are often quite irregular, and may divide off one pole from the rest of the kidney by a groove-like formation of the infarction. On gross section they are, when recent, very soft and even grumous; they are yellow in colour, distinctly wedge-shaped, and often extend several centimeters into the renal parenchyma. Later they become gradually whiter as the process of organization proceeds. Except when very recent they have no haemorrhagic zone demarcating them from the renal parenchyma. On microscopic section these infarcts present tissue in a state of complete anaemic necrosis, the renal cellular elements are no longer distinguishable, and scattered through the field are numerous amber-coloured asterisk-like crystals about the size of a red cell. Beyond this the kidney of chronic bacterial endocarditis shows grossly nothing more than an occasional petechia on the mucous membrane of the pelvis. I have never seen one of the flea-bitten kidneys described by Horder. The blandness of the infarctions is entirely dependent upon the non-pyogenic properties of the infecting organisms. These non-suppurative infarcts are the only variety associated with chronic bacterial endocarditis. To me they are grossly indistinguishable from the infarcts found in the kidneys of chronic rheumatic (?) endocarditis, except that they are usually more recent (i.e. yellower) and are a more constant feature. In fact it is rare to find chronic bacterial endocarditis without renal infarcts.

Microscopic studies of the kidneys of chronic bacterial endocarditis have revealed facts of great import. In 1910 Loehlein (21) described lesions which he called embolic focal nephritis; these were further studied and verified during the next two years by Aschoff (32), Gaskell (22), and Baehr (23).

According to Gaskell the glomeruli are characteristically altered and greater or less numbers are affected. Only some capillary tufts of a single glomerulus may be affected. The altered capillaries are swollen and the tufts may contain fibrinous exudate which may extend into the space between the glomerulus and Bowman's capsule, forming with the cells desquamated from the visceral epithelium crescentic formations similar to those seen in subacute glomerular nephritis. There is leucocytic infiltration of the affected part, which may later involve the para-glomerular tissues and, becoming lymphocytic, pass into hyaline-like tissue. According to Baehr these changes are found in all stages in the same section. Baehr lays particular stress upon the end stage, which produces hyaline-truncated pyramids of a portion of the glomerulus.

Libman claims that the lesions are pathognomonic of chronic bacterial endocarditis, and is able to definitely decide that a sclerotic heart-valve is that of



healed bacterial endocarditis if he finds these lesions in the glomeruli. Analysis of the reports of kidneys of chronic bacterial endocarditis in which characteristic embolic focal nephritis was found shows the following:—

TABLE IX.

	No. of Cases.	Renal Histology.	Bacteriology of Blood.
Loehlein . . .	8	Characteristic renal lesions	—
Gaskell . . .	3	"	"
Baehr . . .	25	Characteristic renal lesions in 23; normal kidneys in 2	Endocarditis cocci
	1	Lesions not characteristic	Gonococci "
	1	" " "	B. influenzae
Thalhimer . .	1	" " "	" "

### *Pathology of the Brain.*

Simmonds (31), reporting from the Eppendorf Hospital of Hamburg, has recorded the findings in seven patients dying of cerebral haemorrhage in contradistinction to embolic cerebral softening during the course of endocarditis. He was careful to eliminate from his list apoplexies occurring in patients whose hearts present signs of recent endocarditis (tiny vegetations), frequent causes of which are carcinosis, phthisis, chronic cystitis, chronic renal disease, and old nerve lesions. These are to be looked on rather as morantic or terminal endocarditis.

TABLE X.

### *Simmonds's Brain Autopsies in Endocarditis.*

Clinical Diagnosis.	Autopsy—Brain.	Bacteriology.	Autopsy—Heart.
I. Brain tumour in 11-year-old girl	Right hemisphere, egg-sized blood clot—ruptured into ventricle. Pea-sized pial aneurysm—another aneurysm of left side. Bean-sized occipital haemorrhagic cyst	Aneurysm and valves showed Gram-positive. Cocci in sections	Verrucous endocarditis of mitral and left auricle
II. 10-year-old boy. Chronic otorrhoea. Brain abscess	Egg-sized fresh blood clot, left occipital lobe ruptured into ventricle. Pea-sized pial aneurysm	Same as above	Mitral and left auricular verrucous endocarditis
III. Moribund woman, 32 years	Haemorrhage into forebrain due to rupture. Pea-sized right sylvian aneurysm	No cocci found	Old and recent verrucous endocarditis of mitral
IV. Woman, 27 years. Chronic endocarditis. Apoplexy	Left hemisphere, child-fist-sized haemorrhage. Aneurysms, hazel-nut-sized at junction of vertebral arteries. One pea-sized of right sylvian artery. Two lentil-sized near right sylvian artery	Same as III	Old and recent vegetations of aortic and mitral valves with calcification
V. Woman, 50 years. Apoplexy	Haemorrhage right cerebral hemisphere	Same as III	Severe old recurrent mitral endocarditis
VI. Man, 32 years. Chronic endocarditis. Apoplexy	Cerebral haemorrhage	Same as III	Endocarditis
VII. Man, 45 years. Chronic endocarditis. Apoplexy	Fist-sized cerebral clot.	Same as III	Aortic endocarditis

Simmonds has shown in this analysis that not only areas of softening but cerebral haemorrhage may be caused by endocarditis alone. In the first four cases he was able to show definitely that these haemorrhages were not due directly to embolism but to rupture of embolic aneurysms of the vessels of the brain and pia mater. These aneurysms are the embolic aneurysms discussed above as occurring only in chronic bacterial endocarditis. In the first two cases the bacteria were shown in the valves and the aneurysms. In the third and fourth cases they were not demonstrable. (See discussion of healed and healing lesions above.)

That these brain lesions are not uncommon in bacterial endocarditis is shown in the analysis of Horder's cases.

TABLE XI.

In 19 of 150 cases there were noted the following symptoms of involvement of the brain :—		In 14 of 118 post-mortems the following lesions were noted :—	
Hemiplegia :		Multiple haemorrhages :	
Right side . . . . .	9	Into meninges . . . . .	10
Left side . . . . .	8	Into brain . . . . .	4
Right side followed by left side . .	1		
Sudden death :			
(Autopsy showing extensive sub-arachnoid and intrapontine haemorrhages) . . . . .			
	1		
	19		14

Nine years after Simmonds's report Schottmüller (25) from the same hospital reported the following neurological lesions in chronic bacterial (*streptococcus viridans*) endocarditis :—

<i>Clinical.</i>	<i>Pathological.</i>
Basal meningitic signs with convulsions.	Haemorrhage at the base and into the lateral ventricle ( <i>streptococcus viridans</i> ).
Increasing deafness.	Right temporal and right occipital meninges show dollar-sized areas of haemorrhage.

#### *The Clinical Features of Bacterial Endocarditis.*

The symptomatology of bacterial endocarditis agrees very well with its pathology. For this reason the relation between these two factors will be entered into in the course of this discussion.

Before beginning it should be well understood that bacterial endocarditis usually occurs with involvement of only some of the systems or organs to be detailed. In other words, the student need not expect to find all the clinical features here enumerated in any one case, nor even until he has seen a very

large number of cases. The discussion of what constitutes the clinical syndrome necessary for the diagnosis of bacterial endocarditis will be left to the section on diagnosis.

It should be remembered before entering upon this description, first that bacterial endocarditis is a bacteraemia in which the primary localization is upon the endocardium, and from this the continuous or intermittent infection of the blood-stream proceeds. To be sure, the primary infection has entered the body and has been carried to the endocardium by way of the blood-stream.

On the contrary, there are cases in which the primary infection of the blood is the main feature, the endocarditis being secondary in importance and often undiagnosable before autopsy. Consequently we have two main features: first, the endocarditis; and secondly, the bacteraemia which results in toxæmia and embolic or focal lesions and symptoms.

The portals of entry of the infections are in many cases clear and in many vague. The acute cases are likely to have the skin as an entrance-point, especially in staphylococcic cases. In many of these cases the diaphyseal marrow of the long bones is infected, and the disease begins as an osteomyelitis and is followed by endocarditis. In streptococcus pyogenes cases the mucous membranes of the throat and the puerperal uterus offer portals of entry. The gonococcus is by no means the only organism that invades the blood by way of the genito-urinary tract; many staphylococcaemias and streptococcaemias have as their origin instrumentation of this tract. The pulmonary tract gives entry to the pneumococcus. In chronic bacterial endocarditis the streptococcus viridans unquestionably enters during the repeated attacks of tonsillitis which are forerunners of all these cases.

*Onset.* This is of course very rapid in acute endocarditis. The picture is usually ushered in by a chill, malaise, fever of 104 degrees and great prostration. The picture may at times be very fulminating and the toxæmia so great as to make it impossible to get a history directly from the patient.

In chronic endocarditis the onset is very insidious, reminding one at times of typhoid fever. For weeks the patient may complain of severe malaise, headache, and have chilly feelings or even sporadic chills.

*Physical signs.* Very small pustules, a little larger than a pin-head, are occasionally found in the hairy parts of the scalp in staphylococcus aureus cases.

Oedema of one or both conjunctivæ is a rare lesion, and is usually to be considered as a sign of thrombosis of the cavernous sinus. The oedema is somewhat red, but has not the redness of acute inflammation. It extends up to the sclero-corneal junction. The oedematous conjunctiva protrudes between the lids.

Pan-opthalmitis is not an uncommon lesion in streptococcus pyogenes cases. It may be bilateral. Retinal hæmorrhages are a very common feature of both the acute and (more so) of the chronic cases. It is surprising that Horder only notes it in five of his 150 cases, as it is rare to find a case of chronic bacterial endocarditis in which retinal hæmorrhages are not found at some time,

if the eyes are repeatedly examined. These haemorrhages may be small pin-head-sized spots or haemorrhagic splotches. At first bright red, they soon become dull, and in a few weeks are absorbed. White spots also occur concomitantly.

Suppurative thrombosis of the lateral sinus may at times precede and be the cause of acute endocarditis. It is usually streptococcic.

Nasal lesions are very rare. Lenhartz reports an acute case in which a massive haemorrhage occurred into the subcutaneous tissue of the nose. It was a streptococcic lesion.

Petechiae of the mucous membranes are common lesions in bacterial endocarditis, especially in the chronic cases. They are, as a rule, small, measuring 1-2 mm. in diameter, round or oval, and usually multiple. At times they show a white centre surrounded by a red area, which is sharply demarcated from the surrounding normal mucous membrane; at other times they are merely red. They are never painful or tender and are not elevated. They are probably embolic, and the whitish centres represent the anaemic area.

The most frequent site is in the mucous membrane of the lower conjunctivae, the roof of the hard palate, the insides of the upper and lower lips and of the cheeks.

*Nervous system.* Delirium is a common feature of acute endocarditis when the toxæmia is great. Acute meningitis may occur in the acute streptococcus and pneumococcus cases. In the chronic cases focal symptoms in the nervous system are among the commonest findings. They occur as pareses, which may recover completely during the long course of the disease, or as paralyses. Those referable to the cranial nerves are:—

Oculo-motor nerve	.	External strabismus, dilated pupil, ptosis of the upper lid.
Pathetic	„	External strabismus.
Abducens	„	Internal strabismus.
Facial	„	Facial paralysis.
Auditory	„	Increasing deafness (Schottmüller (25)).
Hypoglossal	„	Hemiparalysis and atrophy of the tongue.

More extensive cerebral lesions occur as monoplegias (rarely), but the most common is hemiplegia.

Basal meningitis with convulsions has been noted in one chronic (streptococcus viridans) case (Schottmüller (25)).

*The skin.* Lesions of the skin are very common in bacterial endocarditis; they occurred in forty-three of 150 cases (Horder). They are usually found as small petechiae (similar to those occurring in the mucous membrane) scattered over the face, arms, back, legs, and chest. They are said to be frequent in the palms and soles, but I have seen them there rarely. They may be very few in number, but on the other hand they may be numerous. They are painless and red, but fade rapidly to a dull brown, and finally before complete absorption resemble freckles—a point of importance, inasmuch as between the appearance

of crops, these freckle-like lesions upon a part of the body not generally exposed to the sun should be carefully scrutinized. They cannot be obliterated by pressure. They are when numerous often agminated. They are by far more common in the chronic cases. In the acute cases large splotchy areas of haemorrhage may occur, commonly on the chest or an extremity.

Other lesions seen in streptococcus pyogenes or staphylococcus aureus cases are vesicles or pustules, which may vary from split-pea size to a centimeter in diameter. Bullae may occur rarely, the clear fluid usually showing streptococci. Lesions similar to erythema nodosum are not uncommonly seen in the soles of the feet in streptococcus cases.

Painful erythematata (*nodosités cutanées éphémères*) of the fingers and toes are almost a pathognomonic sign in chronic bacterial endocarditis. They were first noted by Heubner in 1879 (30), and are only moderately common, although found in seven of ten cases by Osler (6). They are most interesting. Usually occurring suddenly, the patient complains of pain in a toe or finger. On examination there is slight redness and marked tenderness on a lateral aspect of a terminal phalanx of a finger or toe. The pads of the fingers are a favourite site. The redness is not sharply demarcated. Rarely is the redness and tenderness so marked that the tiro would desire to incise it. They have occurred to my knowledge in none but streptococcus viridans and bacillus influenzae cases. They never suppurate. They are usually very ephemeral, passing off in a day or two. They are commonly multiple. They are apparently embolic phenomena in the terminal digital arteries.

Besides actual skin lesions, patients with chronic bacterial endocarditis present a marked subicteric hue, and at times a pallor suggestive of chlorosis or pernicious anaemia. (See diagnosis.)

*Glands.* As a rule glandular enlargement is not an important feature, even in chronic cases, but at times it may be so marked as to simulate leukaemia. The enlargement of the tracheo-bronchial lymph nodes draining the heart is a regular feature, but gives no symptoms.

*Chest.* Libman has laid stress upon tenderness to light percussion in the lower part of the sternum, even before the anaemia is sufficiently developed to account for it. When the anaemia is advanced the dark brownish marrow of regeneration in the hematopoietic system is often found in the sternum (17, 18).

*The heart.* It may seem paradoxical to say that the cardiac signs are the least important in the diagnosis of bacterial endocarditis, but such is the case. There are, as a rule, distinct signs of endocarditis; definitely diagnostic valvular murmurs were noted in 60 per cent. of Lenhartz's acute cases; in chronic cases the murmurs are usually easily attributable to the involvement of a definite valve or valves. However, murmurs may be very slight and resemble a febrile or anaemic murmur, or they may be absent.

Mural abscesses in the heart wall resulting in purulent pericarditis are a common terminal event in staphylococcus aureus cases, and usually give definite pericarditic signs.



One point of extreme importance is the rarity of signs of decompensation in bacterial endocarditis. Lenhartz has noted this. The acute case always dies of toxæmia or of some other cause before great mechanical damage is done to the valves. The chronic case also rarely shows decompensation signs (oedema, ascites, pulsating enlargement of the liver, &c.), even though the disease has lasted more than a year. I have seen very few that have shown this, the patients usually dying of bacteraemia or other causes before this occurs.

Libman has suggested that decompensation does occur in many of the chronic cases after they have become healed (in a bacteriological sense), and that this is one of the modes of death. Certainly his investigations have shown that some cardiacs dying of decompensation have hearts which resemble those of chronic bacterial endocarditis.

*The lungs.* In acute cases due to pneumococcus the lesions of lobar pneumonia (consolidation, pleurisy, empyema, &c.) are very often found; these of course give their typical symptoms. Acute staphylococcus cases are rarely associated with pulmonary symptoms, although the post mortem may reveal furuncles in the lung—usually hazel-nut-sized and scattered through the bases. Puerperal streptococcus cases rarely have pulmonic symptoms. Occasionally, however, lung-abscesses or empyema may develop. Chronic bacterial endocarditis rarely shows any pulmonic signs. In one streptococcus viridans case at autopsy I have seen small, grayish, firmly infarcted areas in the lung. Microscopic section showed nothing but polynuclear infiltration, but no tendency on the part of the lung to break down.

*The liver.* In acute cases there is rarely any enlargement, but at autopsy small multiple abscesses may be found with streptococcus or staphylococcus aureus. In chronic cases the liver may be palpable at times, due to parenchymatous degeneration.

*The spleen.* In acute cases the spleen may be felt; it is usually soft, and rarely extends more than a couple of finger-breadths below the free border. On autopsy it is dark-purplish and soft; it may have macroscopic or microscopic purulent areas.

In the chronic cases the enlargement of the spleen is a fairly constant feature. Such spleens may vary from a few fingers below the costal margin to organs as large as those of polycythaemia or leukaemia. At times attention is attracted to the spleen by the occurrence of acute attacks of left lumbar hypochondriac pain, and rarely friction sounds may be heard at these times over it. The spleen practically always presents at post mortem one or more infarcts, which may be larger than a hen's egg. The tissue of the infarct is yellowish and more or less firm. It never breaks down into pus, but may be grumous, and may become adherent to an adjacent organ (e.g. colon).

*The kidneys.* Acute endocarditis with its suppurative infarcts rarely gives symptoms referable to the kidneys. The urine may be that of an acute nephritis, or may merely be that of a kidney of fever. The bacteria (streptococci, staphylococci) are usually easy to recover from the urine.



In chronic endocarditis the kidney may at times give symptoms of infarction (pain, haematuria). As a rule, however, the infarctions are not noted clinically. The urine during the course of the disease usually contains a trace of albumin and a few hyaline casts. From time to time an occasional red blood cell appears. Occasionally there is macroscopic haematuria. Albuminuria very often follows haematuria. Intermittent albuminuria, according to Horder, should always suggest renal infarction. The streptococcus viridans is cultivated with great difficulty from the urine. According to Libman, bacteriologically healed cases of chronic bacterial endocarditis may die later of uraemia.

*The joints.* In acute endocarditis, due to streptococcus or pneumococcus, there are apt to occur purulent or seropurulent arthritides, those due to the former organism being clinically milder in their course and often going on to spontaneous resolution. The joints most frequently involved in the order of their frequency are—knee, wrist, elbow, ankle, sterno-clavicular, hip, shoulder. In chronic endocarditis fleeting pains in the joints with at times a serous collection of fluid are very common. Horder has recorded pains in sixty-six and swelling in twenty-two of 150 cases. The fluid is usually absorbed spontaneously. The wrist and knee are the joints most commonly affected.

*Extremities.* Acute endocarditis is apt to develop metastatic abscesses. Subpectoral and pectoral muscular abscesses are common in staphylococcus aureus cases. Also in these cases the rectus muscles may develop tender knots which on incision contain pus. The inner aspect of the thighs is not an uncommon site for abscesses of streptococcal origin.

*The blood-picture.* In acute endocarditis the red cells are not usually affected. The leucocytes usually range between 15,000 and 50,000 with high polynucleosis. In chronic cases there is usually an anaemia of secondary type, which may become very profound, the red cells falling to 2,500,000, or even lower, and the haemoglobin to 40 per cent. The white cells range between normal and 12,000 with some polynucleosis. The leucocytosis may at times increase (e.g. during infarction, &c.).

*Clinical course.* The acute cases usually run a very rapid and fatal course, varying between a few days and usually five weeks at most. The patient usually runs a septic chart varying between 97 and 104 or 106 degrees with repeated chills and sweats. The toxæmia is marked, and the patient usually succumbs to it.

In the chronic cases the course varies between a few months and a year or two. The average duration is about six months. The patient usually runs a very intermittent temperature with occasional chills and sweats. At times the fever may abate for weeks and the patient feel well enough to walk around the wards. During all this time, however, the bacteraemia continues and is easily demonstrable, and it is really a remarkable thing to see such patients walking around with 50–100 colonies of streptococcus viridans in every c.c. of their blood. The protracted course is usually terminated by toxæmia. At times an embolism of an important organ (e.g. the brain) terminates the picture.

*Prognosis.* As causes of death in 150 acute and chronic cases Horder records:—

TABLE XII.

Circulatory failure (dilatation of the heart and anasarca)	66
Coma	23
Sudden death (due to embolism, changes in the heart such as rupture of a valve or perforation of the septum, &c.)	19
Uraemia (renal oedema, suppression of urine)	18
Exhaustion	8
Delirium and mania	5
Hyperpyrexia	2

It is unusual to see such stress laid on circulatory failure. I have not seen it very often. Lenhartz and Osler consider its absence a clinical point of diagnostic value. Billings, however, saw it in six of fourteen chronic cases.

In regard to uraemia as a terminal event in chronic cases:—Lenhartz (10) reports (Case 25, p. 405) a streptococcus viridans case of about four months' duration with haemorrhagic nephritis in the last week. (Case 21, p. 405) A streptococcus pyogenes case of about five months' duration with haemorrhagic nephritis in the last week and a half. (Case 31, p. 409) A streptococcus case of five months' duration with terminal uraemia. Horder reports a streptococcus case of two years' duration with terminal uraemia and death. The importance of these cases lies in the fact that cases of chronic bacterial endocarditis must be followed for a long time before cures can be authentically reported.

Do cases of bacterial endocarditis ever recover? It would seem that the prognosis is invariably bad; if not immediately, then eventually. Even though the chronic cases may become bacteria-free and the vegetative lesions on the heart valves undergo retrogressive changes, yet these cases usually die of decompensation due to changes in the valves too great to allow functional adequacy, or a nephritic death ensues due to embolic focal nephritis. However, it may be advisable to quote some authorities in regard to healed cases:—

Jochmann (24) reported in 1912 two recoveries of seven streptococcus viridans cases; one of these had been treated with an anti-streptococcus viridans serum. Also one of three gonococcus cases recovered. These cases are, however, of too recent date to be of value. Libman (18) in 1912 seems to be sceptical even about cases that have become bacteria-free. Lenhartz (3) in 1901 saw an acute post-gonorrhoeal endocarditis recover in twelve days, but there were no blood-cultures in this case, so it might have been an acute non-malignant gonorrhoeal endocarditis. Harbitz (4) in 1899 had ten autopsies on cases with typical heart lesions in a healing or healed stage in which he could find no cocci in sections. Horder (9) in 1909 reports a case of more than eight weeks' duration with two negative blood-cultures, which recovered and is the only one of his series of 150 cases that did recover.

*Diagnosis.*

In view of the vast symptomatology of bacterial endocarditis, especially of the chronic variety, it may be advisable to discuss what criteria are necessary for such a diagnosis. To begin with, in acute bacterial endocarditis three factors are necessary: (1) Fever and demonstrable bacteraemia (positive blood-culture); (2) a cardiac murmur; and (3) peripheral symptoms (e.g. embolism, petechiae, &c.). Can the diagnosis be made without one of these three? It can, but with difficulty. Cases of mural endocarditis may have no murmur and hence the diagnosis can be only suspected. The fever may be absent for some time. The bacteraemia is rarely absent. I used to think that every case of chronic bacterial endocarditis had bacteria in the blood-stream which could be cultivated after single, or certainly after several, attempts at blood-culture. Recently Libman's investigations have shown that some cases, which he calls 'healing or healed', are bacteriologically negative during life. It is probable that many of our cases of chronic endocarditis with fever fall in this category. Certainly a bacteraemia is no necessary accompaniment of embolic symptoms, as chronic endocarditis with calcific deposits in the valves can be associated with showers of petechiae with the blood-stream negative to culture. Are peripheral symptoms necessary for a diagnosis of bacterial endocarditis? They are unquestionably of more importance than the constitutional or the cardiac symptoms. I cannot recall a single case in which embolic phenomena did not appear at some stage of the disease. They are really the *sine qua non* of diagnosis.

*Differential Diagnosis.**I. Febrile systemic pictures (fevers of doubtful origin).*

1. Typhoid (including paratyphoid) fever. This is probably the one disease for which bacterial endocarditis, especially the chronic variety, is most often mistaken. The blood-culture and the agglutination tests against *B. typhosus* and *B. paratyphosus* A and B will of course clear up the diagnosis. Late in the disease the picture may simulate post-typhoid sepsis, especially if there are involvements of small joint foci; but it is safe to say that in a typhoid (?) case which has not become normal in eight weeks there should be strong suspicion as to the correctness of the diagnosis.

2. Rheumatism. When this appears in the subacute type with repeated relapses and recrudescences of subacute arthritis it is most puzzling, especially as the cases usually have an endocarditis. Here the blood-culture is of utmost service. The leucocytosis in these cases is usually lower than in bacterial endocarditis, but I remember a case of this type in which the leucocytes ranged around 50,000 and there were repeated joint effusions which would subside without much pain; in the presence of negative blood-cultures the salicylates were pushed to the limit and the patient recovered.

Of great difficulty in differentiation are the fulminating attacks of rheumatic endocarditis, or as Lenhartz has called it, the malignant type of rheumatic fever. These cases are extremely rare, but resemble closely acute bacterial endocarditis. They usually die rapidly of the toxæmia. They are not associated with petechiae and have negative blood-cultures.

Very puzzling at times are the chronic cardiacs with tuberculous or gonorrhoeal arthritis and fever. The tuberculin reaction may be of service; when there is no urethral discharge complement-fixation tests upon the blood for gonorrhoeal antibodies are of value.

Chronic rheumatic endocarditis with fever and petechiae is a type that cannot be clinically differentiated. These cases were formerly thought to be separable from chronic bacterial endocarditis, because they presented negative blood-cultures. Libman's work leads one to believe that they are healing or healed cases of chronic bacterial endocarditis. The relation between calcified heart valves and petechiae has been discussed.

3. Tuberculosis. Acute general miliary tuberculosis offers the utmost difficulty in diagnosis. Of course it has negative blood-cultures. Pulmonary signs are rare in endocarditis. The eye-grounds may offer the solution, as the choroid tubercle, though rare in this disease, is distinctly different from the retinal haemorrhage of endocarditis.

Chronic glandular tuberculosis, especially of the bronchial and mesenteric lymph-nodes as it occurs in children (29), may be puzzling. It may be of service to note the age of the occurrence of bacterial endocarditis. I have never seen a case under 16 years of age.

Acute pulmonary tuberculosis may offer difficulty. I remember a case in which a patient in whom this condition was healing began to run temperatures and have chills and sweats, and experience attacks of left lumbar pain. This was naturally attributed to a recrudescence of his tuberculosis and a new focus in the left kidney. Blood-culture, however, showed *streptococcus viridans*, and the autopsy showed an area of moderately active tuberculosis of the right apex—a bacterial endocarditis, and infarcts in the kidneys and spleen. A very recent one in the spleen probably accounted for the abdominal symptoms.

4. Malaria. This disease should never be forgotten and can at times be diagnosed only after most thorough and repeated blood examinations. The chronic types in which there is some pigmentation of the skin, an enlarged spleen, and anaemia may be very puzzling when they begin to run irregular fever. Aestivo-autumnal fever should be remembered.

5. Ambulatory cases. These often form the material of the coroner's autopsy table. I have seen cases that were killed by accident in the streets in which the autopsy showed that they had been working for some time with active cardiac lesions and fever. This no doubt accounted for their lack of agility at the time of the fatal accident.

6. Hepatic suppuration. Pylephlebitis usually gives chills, fever, sweats, and profound toxæmia. The aetiology (appendical or other suppuration in the

region of the portal tributaries) usually suggests the diagnosis—most of them are post-operative. Blood-culture is always negative, unless there is a communication of a hepatic abscess with the hepatic veins (a great rarity).

Septic cholangitis is often a puzzling condition. In the intermittent ball-valve stone cases with chills, fever, and sweats, in case the skin is only subicteric and the pain not a marked feature, the diagnosis may be difficult. The tendency to haemorrhage into the skin in these cases makes them simulate a bacteraemia.

Solitary hepatic abscess may give much trouble in diagnosis. Its differentiation depends on finding hepatic enlargement and the aspiration of the pus.

7. Pyelitis. This condition as it occurs in children (33) hardly ever simulates endocarditis. In adults, when associated with stone, the chills, fever, and sweats are of importance in cases where there is little abdominal or lumbar pain and where there is little in the urine except a bacteriuria.

## *II. Non-febrile systemic pictures.*

1. Diseases of the haematopoietic system. One of the most frequent mistakes in diagnosis is to consider the chronic forms chlorosis. The peculiar pallor in a young person, the pulsating veins in the neck, the secondary anaemia, the general weakness, and the cardiac murmur give much ground for such a mistake when a case is hurriedly examined in a dispensary and the temperature happens to be normal.

I have seen the diagnosis anaemia gravis carefully considered in a young man in whom the red blood-count was 1,250,000 and the haemoglobin too low for pernicious anaemia. It required the post-mortem table to elucidate the matter as a case of healed endocarditis. He had repeatedly negative blood-cultures.

Early Hodgkin's disease and splenic anaemia often enter into question in cases with anaemia, glandular enlargement, and palpable spleen. Often it requires fairly long-continued observation to clear up the situation.

2. Uraemia. The cases of healed chronic endocarditis which die of uraemia are really beyond clinical diagnosis.

3. Brain involvement. Simmonds's reports show cases of cerebral haemorrhage due to chronic bacterial endocarditis which were diagnosed as brain-tumour or brain abscess by competent authorities.

The apoplexies in this disease are no different clinically from those in ordinary chronic endocarditis. The presence of anaemia and petechiae or haemorrhage of the fundi oculorum sets matters to rights and blood-culture is then indicated. Fever is of no value as it may occur in any brain insult.

Focal involvement of single nerves (especially cranial) is much more common in chronic bacterial endocarditis than in any other form of heart disease.

## *III. Clinical pictures overshadowed by focal involvements.*

1. Gynaecological conditions. Abdominal pain with some palpable changes in the pelvic organs has, in my experience, been a pitfall for more than one gynaecologist. In one case a tube was removed and the patient was sent to the



medical side after petechiae had developed. In another case only the fever and enlarged spleen (thought to be malaria) prevented a gynaecological operation.

The inadvisability of removing gonorrhoeal adnexa in an active stage of inflammation was shown in a case in which the abdominal wound was completely healed before chills and sweats announced the onset of a gonorrhoeal endocarditis. The gonococci were cultured from the circulating blood and the patient succumbed in a few weeks.

2. Cases with cardiac decompensation. As was noted before, this is a rare form of death in this disease while there is active bacteraemia. After the latter has disappeared these cases cannot be distinguished except by autopsy from other chronic cardiacs with decompensation.

3. Crises of abdominal pain. Renal infarcts have, as a rule, given little or no pain. In one case, however, the attention was so closely directed to one kidney that the surgeon removed it, considering it unilateral septic infarction. The pathologist in the operating room elucidated matters. The autopsy showed typical lesions in the heart and embolic aneurysms in the splanchnics. Fever and pain in one loin have been mistaken for renal tuberculosis, in the case of a large splenic infarct which had become adherent to the colon, causing a localized aseptic plastic peritonitis. The case was one of chronic bacterial endocarditis.

4. Femoral aneurysm. In a case of embolic femoral aneurysm in which the thigh was two or three times the normal size, a diagnosis of metastatic hypernephroma was at first entertained, as the kidney could be felt enlarged. This case went to the post-mortem table before the matter was cleared up. Chronic bacterial endocarditis was carefully considered, but the blood-cultures were repeatedly negative. The anaemia was so intense that malignancy was considered almost a certainty (femoral sarcoma or hypernephroma). The autopsy revealed a huge aneurysm which had almost completely eroded the femur. Healed lesions of chronic bacterial endocarditis were found in the heart.

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## AGGRESSINS IN APPENDICITIS AND SOME OTHER VARIETIES OF PERITONITIS

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### *Introductory.*

IN its widest significance the term Aggressin implies any substance formed in the process of bacterial growth which aids the organisms in their attack upon living tissues. Theoretically such a substance may act by antagonizing any one or more of the processes which together form the whole mechanism of immunity. In this paper we are concerned only with substances, of an unknown composition, which inhibit phagocytosis *in vitro*.

The first worker to study the subject was Bail, who came to the conclusion that the formation of aggressins is of fundamental importance to the process of general infection. Following Bail many investigators have confirmed the existence of these substances, but most have disagreed with him concerning their origin and importance.

It is not proposed to discuss the subject from a general point of view in this paper, since it is of no great importance to our subject how the chemical bodies which inhibit phagocytosis are formed; whether they are excreted by living bacteria, or formed from the tissue fluids by bacterial action, or, finally, arise as the result of bodily disintegration of the organisms.

It may be said, however, that the experiments here described strongly suggest that, at least in the fluids dealt with, the inhibitory substances are the result of bacterial break-down; for a marked degree of inhibition is seldom to be found in recent exudates, however free the growth of organisms may be, but it is far more commonly shown by exudates of longer standing, such as true appendicular abscesses with a history of many days' illness. These fluids are usually swarming with bacteria, of which large numbers are undoubtedly dead.

The subject of aggressins has been reviewed from a general point of view by Levaditi (8), and more recently Dudgeon (4) has made an experimental study of it. The latter examined a large number of spontaneous and artificial exudates from the human subject and from laboratory animals respectively. He demonstrated the aggressive action of fluids obtained from many varieties of pus by filtering or centrifugalizing, and he investigated the specificity of the aggressins contained in the fluids.

He found that in practically all the human exudates investigated, bacterial specificity was absent. That is to say, if an exudate was found to inhibit the phagocytosis of *Staphylococcus aureus* (the infecting organism), it would also inhibit the phagocytosis of *B. coli* and *Streptococcus pyogenes*.

He believes, with many previous workers, that the aggressins exercise their main action upon the opsonins of the serum, and that their influence upon the phagocytes is of secondary importance.

F. H. Thiele and D. Embleton (12) have recently published some experiments in which, among other things, they demonstrated in inflammatory exudates the presence of protein break-down products, which they believe to have a strong toxic action upon the organism in general, and more particularly to act aggressively with regard to phagocytosis. They advance the theory that it is the digestion of the bacterial protoplasm by anti-bacterial ferments which gives rise to these chemical bodies, and they maintain paradoxically that the virulence of a bacterium depends upon the degree of digestion which it undergoes. However this may be, it is quite probable that the products of proteolysis may play a very important part in the inhibitory action of aggressive inflammatory fluids, whether the broken-down proteins originate from the bacteria or from the leucocytes.

Up to the present no attempt appears to have been made on any considerable scale to correlate the opsonic or aggressive properties of human inflammatory fluids with the clinical course and outcome of the infection.

The experiments described below were therefore undertaken with this purpose, and infections of the peritoneum, particularly those accompanying acute appendicitis, from their frequent occurrence and varying severity offered a suitable field for investigation.

#### *Methods.*

The material used in these experiments consisted of some sixty to seventy specimens of exudates from the peritoneum, which were collected at the time of operation. Of these the great majority were from cases of acute appendicitis in all its stages.

In some cases, where tube-drainage had been employed, further specimens of pus were obtained with a sterile pipette from the bottom of the tube at varying intervals after the operation. But experiments made with these samples must be considered as of doubtful value, seeing that the tube itself acts as a foreign body, and must cause a local disturbance in the course of the inflammatory reaction.

Each exudate was subjected to a bacteriological examination, both microscopically and culturally. Only aerobic culture-methods, however, were employed, since the separation of the anaerobic organisms in such highly mixed infections as are usually encountered in perforative peritonitis is a long and tedious operation; nor was it thought necessary to the aim of the investigation.



Full accounts of the anaerobic organisms occurring in appendicular peritonitis have been given by Tavel and Lanz, Heyde, and others. Table IV shows what bacteria were found in the exudates. It will be seen that in a very large majority of the mixed infections diplo-streptococci were encountered.

Some twenty-two strains of this organism were tested in a large variety of culture media, particularly for acid formation in sugars, and the data thus obtained are given in Table V. The great majority of the strains fail to identify themselves with any of Gordon's named varieties of streptococcus, and moreover, as Ainley Walker has shown, their sugar-fermentation reactions are very liable to alter after passage through animals, or after prolonged growth on artificial media.

It appears that these streptococci do not play any important part in the primary infection; but I have had two cases in which they were found in secondary or residual infections after the *B. coli* had disappeared or died out.

*Exudates.* Fluid free from cell-débris and bacteria was obtained from the samples of pus by means of a centrifuge; or, in some cases when the pus was very thick, by filtering under pressure through a small Doulton's candle.

In some cases a portion of this was heated to 60° C. for 15 minutes, in order to destroy any opsonin which it might contain.

All exudates thus prepared were kept in the ice safe till the time of the experiment.

A few cases provided two distinct varieties of fluid; usually a small collection of true pus separated by a well-defined capsule from a surrounding clear or turbid fluid. Here two specimens were collected and tested separately.

*Serum.* Normal serum was obtained fresh for each experiment, and always from the same individual (A. D. G.); while in a certain number of cases some blood was drawn from the patient, and a parallel series of tests was carried out with the serum. Care was taken that all the sera used in an experiment had been kept for exactly the same length of time, and at the same temperature.

*Leucocytes.* Human white cells were used in all experiments. Twenty to thirty drops of blood were run into a centrifuge tube containing about 10 c.c. of a 0.9 per cent. citrated saline solution. The mixture was centrifugalized, and the corpuscular deposit was twice washed with normal saline and re-centrifugalized. The upper layers of the final deposit were pipetted off and used in the experiment.

*Bacteria.* A stock strain of *B. coli*, which had proved itself fully susceptible to phagocytosis, was employed in the great majority of experiments. In a few, some other organism, such as *Staphylococcus aureus* or a streptococcus, was used, either alone or in conjunction with the *B. coli*.

A suitable emulsion of the bacteria was prepared by suspending in normal saline a 24-hour (or less) culture on agar. Most strains of *B. coli* will in five or six hours produce a sufficiently profuse growth on agar at 37° C. If the culture is to incubate for twenty-four hours, it is best to keep it at 25° C., for the individual organisms tend to grow to a larger size at the lower temperature,

and they are therefore easier to count when they have been ingested by the phagocytes.

The thickness of the emulsion may, after some practice, be judged by the eye, but it is far better to corroborate this by performing a preliminary experiment with normal serum, phagocytes, and bacterial emulsion. This is carried out in exactly the same way as the main experiment, and a stained film is made. A convenient strength for the *B. coli* emulsion was found to be that which allowed each phagocyte to ingest three to five bacteria. Satisfactory emulsions of streptococci are difficult to obtain, for most strains, particularly those grown from peritoneal pus, have a strong tendency to form clumps. Moreover, they are liable to spontaneous phagocytosis in the absence of opsonins. They were therefore seldom used in these experiments.

*Experiment.* Mixtures of the phagocytes, the bacteria, and the various fluids to be tested, were made in a Wright's capillary pipette in the usual way. The contents of the pipette were well mixed by blowing out on to a ground-glass plate and sucking in again. Finally, the open tip having been sealed in the flame, the pipette was incubated for exactly fifteen minutes at 37° C. This procedure was repeated for each fluid, and for the proper number of controls.

*Controls.* Normal serum diluted with an equal quantity of 0.9 per cent. saline acted as the standard with which the mixture of normal serum + exudate was compared.

Where immune serum (i. e. the patient's serum) was also tested, a similar control was employed.

In order to exclude the occurrence of spontaneous phagocytosis, each experiment included a tube containing only saline, phagocytes, and bacteria.

Unless good phagocytosis occurred in the serum control, and unless it was quite absent in the saline control, the experiment was rejected as untrustworthy.

*Stained preparations.* These were made by breaking off the tip of the pipette, blowing the contents on to a slide, mixing well, and allowing the mixture to flow all over the surface—excess of the fluid was rapidly drained off on to blotting-paper, and the slide was dried with gentle heat. The films were haemolysed by dipping once into tap water, dried again and stained for two minutes with carbol thionin.

In counting the stained preparations all clumps of more than two white cells were passed over. Only definite polymorphonuclear cells were counted, and any cell whose content was doubtful, owing to ingestion of dirt or for other reasons, was neglected.

A typical experiment is shown here.

Materials used	Exudate	.	.	.	J. N.
	Serum	.	.	.	normal human
	Leucocytes	.	.	.	" "
	Bacteria	.	.	.	<i>B. coli</i>
	Normal saline.				

<i>Experiment.</i>	Cells counted.	No. of Bacilli.	Blanks.
1. Normal serum + saline + leucocytes + <i>B. coli</i> . . . . .	50	147	8
2. (Normal serum + exudate J. N.*) + leucocytes + <i>B. coli</i> . . . . .	50	21	36
3. Saline + exudate J. N. + leucocytes + <i>B. coli</i> . . . . .	50	14	37
4. Saline + saline + leucocytes + <i>B. coli</i> . . . . .	50	7	46

One volume of each constituent always taken.

\* Brackets represent incubation for one hour at 37° C.

The ratio of the number of bacteria ingested by fifty cells in No. 2 to the number ingested in No. 1 is  $\frac{21}{147} = 0.14$ , and it represents the effect of the exudate on normal serum. This ratio I have called the 'index' throughout the experiments.

In different exudates the index varies between 0 and 1.5, the former showing the maximum of aggression, the latter indicating a definite increase of opsonic action.

No. 3 in the experiment shows the action of the exudate alone, as compared with normal serum.

In this particular case the fluid is devoid of opsonin, but many fluids have a strongly opsonic power, and, as Dudgeon has shown, an exudate may exhibit both aggressive and opsonic activity.

Heating to 60° for fifteen minutes (Dudgeon) or filtering through porcelain increases the inhibitory power of most fluids; for heating inactivates the opsonins, and the filter retains them to a greater or smaller degree (9), with the result that all aggressive bodies present are free to act on the serum opsonins. But in order to maintain natural conditions as far as possible, I have used the unheated exudate in calculation of the index. Tables I to IV show the indices determined in fifty-three cases; I, II, and III dealing only with appendicular peritonitis.

The indices really present an unbroken series from 0.0 (maximal aggression) to 1.5 (supernormal opsonic action), but for purposes of convenience I have classified them as—

- I. Marked aggression (index 0.0 to 0.3);
- II. Moderate or feeble aggression (index 0.3 to 0.7);
- III. No aggression (index 0.7 and over).

#### *Results of Experiments.*

Table I clearly shows that all varieties of appendicular exudates may possess highly aggressive powers. It includes three cases with so short a history as thirty-six hours, as well as a number of abscesses of six to fourteen days' duration. All these exudates were opaque and contained considerable quantities of solid matter (leucocytes, &c.). Most of them were offensive.

It is important to notice that half of the whole number of abscesses tested are included in this table (seven of the total of fourteen). Moreover a glance at

Table II tells us that six more abscesses showed lesser degrees of aggressiveness, while only one abscess-exudate appears in Table III A to be devoid of this property.

The great majority, then, of appendicular abscesses contain pus which exercises an inhibitory action upon phagocytosis. But it is clear that a firm and definite localization of pus is a reaction of the utmost value to the patient, and once the barrier has been erected between the inflammatory focus and the surrounding tissues, the properties of the pus within the walls is of little moment.

TABLE I.

Cases showing a high degree of aggression.

*Index 0.0 to 0.3.*

Abscesses . . . . .	7	Died 1* = 14.3 % mortality
'Free' exudates, not generalized . . . . .	7	Died 2 = 28.6 %
General peritonitis . . . . .	2	Died 2 = 100.0 %
Total . . . . .	16	Died 5 = 31.2 % mortality

\* This case receives special mention in the text.

Supposing, however, that the abscess wall is broken, either by rupture or during operative treatment, then there is poured over the healthy peritoneum a fluid, usually swarming with bacteria, which can paralyse what is probably the most important protective mechanism of the body. This point will be referred to again, when the practical results of the experiments are considered, but it may be well to point out here that the only fatal result of operation upon an abscess, in the whole series of cases, is one where the abscess was opened and drained across the peritoneal cavity (Table I).

Of the nine cases in Table I which showed a condition other than that of abscess-formation, four ended fatally, two being cases of 'general peritonitis', i.e. infections of the whole or a large area of the peritoneum, while the other seven showed varying extent of infection. A precise classification of such cases is not possible.

It is evident that the mortality in this class is very high (44.4 per cent.), and that it compares most unfavourably with the mortality figures drawn from the same class of cases in Tables II and III A together (5 per cent.).<sup>1</sup>

It follows from these considerations that free peritoneal exudates, which are to a high degree aggressive, are a greater menace to the life of the patient than those which exhibit only moderate aggression or none at all.

TABLE II.

Cases showing a moderate or slight degree of aggression.

*Index below 0.7 and above 0.3.*

Abscesses . . . . .	6	Died 0 = 0.0 % mortality
'Free' exudates, not generalized . . . . .	6	Died 0 = 0.0 % "
General peritonitis . . . . .	0	Died 0 = 0.0 % "
Total . . . . .	12	Died 0 = 0.0 % "

<sup>1</sup> It is hardly necessary to add that these percentages, being calculated from such a limited number of cases, can only be taken as a very rough estimate of the true quantities.

An exudate which is thick and offensive is nearly always found to be aggressive.

Table II contains six abscesses and six non-abscess cases. Among the abscesses are to be found three early ones, with histories of only four or five days' illness, whereas Table I (strong aggression) includes only a single abscess of less than seven days' history. Evidently, then, the younger the abscess the less aggressive are its contents likely to be. This holds good up to about the seventh day; after which time aggressin formation may either progress or remain stationary. Now since the early stages of an abscess show only moderate aggression, while its later stages usually show marked aggression, we may conclude that the process is a progressive one, and that, at the very outset of the process, little or no aggression would be found. That this is actually so is demonstrated in Table III A; for here the earliest exudates of all are to be found, some of which must correspond to the pre-abscess condition, and none shows any aggression.

In contrast to this, we have seen in Table I that an exudate as young as thirty-six hours may be highly aggressive, and in these cases adhesion formation is absent, and the condition appears to be the precursor of a diffuse peritonitis rather than an abscess. The conclusion we can draw from these facts is that abscess-formation occurs only in the absence of aggressins. If aggressins are formed very rapidly, owing to a large dosage of bacteria through a severely damaged appendix, then the formation of an abscess seems to be prevented.

Table II happens to contain no cases of general peritonitis, which probably accounts for the extremely favourable mortality figures. However, the 'free exudates' class shows an obvious improvement upon Table I.

TABLE III.

## (A)

Cases showing no aggression. Fluids either inert or possessing opsonic power.

*Index from 0.7 to 1.5.*

Abscesses . . . . .	1	Died 0 = 0.0 % mortality
'Free' exudates, not generalized . . . . .	11	Died 0 = 0.0 %
General peritonitis . . . . .	3	Died 1 = 33.3 % } 7.1 % mortality
Total . . . . .	15	Died 1 = 6.6 % mortality

## (B)

Cases of 'septicaemic peritonitis' caused by streptococcus or pneumococcus in pure culture.

*No aggression.*

General peritonitis . . . . .	3	Died 2* = 66.6 % mortality
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\* N.B.—Two streptococcal cases—both died. One pneumococcal case—recovered.

Tables III A and III B include instances of every variety of case, from a thirteen-hour diffuse peritonitis to a five-day abscess.

In considering what conclusions are to be drawn from this series, the three cases in Table III B must be dealt with separately, for they really stand in a class by themselves. In all three the causative agent of the peritonitis was



a coccus in pure culture; two provided pure cultures of streptococcus, and one gave the pneumococcus. Nor did stained preparations of the pus in any case show more than the single organism.

The appendix was in no case severely damaged. Inflammation of the organ was present in two of the cases, but it was not noticeably more intense than that of the neighbouring intestines. In the third, no lesion of the appendix was evident. Nevertheless, both streptococcal cases terminated fatally with symptoms of a profound septicaemia, while the other patient recovered only after a very severe illness.

There is no doubt, then, that these three must be relegated to the class of 'septicaemic peritonitis', in which the appendix plays no important part (5).

As the table shows, the exudates exhibit no vestige of aggression in the phagocytosis test, and this might surprise us, were the cases of an ordinary type. But if the peritonitis were but the local manifestation of a general septicaemia, there would be no reason to expect such a local concentration of bacteria as might lead to aggressin formation. The streptococci and pneumococci in the exudates under consideration were present relatively in much smaller numbers than are the organisms in the ordinary appendicular cases.

We may judge then that inhibition of phagocytosis is not used as a weapon of local attack by these cocci of high virulence.

Turning now to Table III A, we see that, apart from one early abscess of five days standing, all other cases in the table are in the non-abscess class.

Of the three cases called 'general peritonitis' one died (compare Table I, two cases, two deaths). Of the remaining eleven, all recovered well and rapidly.

It will be seen, then, that the mortality of all non-abscess cases in this table (7.1 per cent.) is much lower than the mortality shown in Table I for similar cases (44.4 per cent.), or in Tables I and II together (26.6 per cent.).

So we may conclude that an unlocalized peritonitis is less dangerous when the exudate is free from aggressins than when it contains them.

Sometimes it is possible to predict with some assurance the outcome of the case examined. For instance, in a generalized peritonitis the presence of aggressins in high concentration practically constitutes a death sentence; for the methods of operative treatment commonly employed do not avail to save the patient's life.

Again, at the opposite end of the scale, an unreservedly favourable prognosis is justified when an exudate, confined to the region of the appendix, is found to be completely free of aggressins. Such exudates are never offensive and are often clear and watery, a quality which may be taken as a guarantee for the absence of aggressins. In the whole range of cases which lies between these two extremes, no confident individual prognosis is possible, since the issue is obscured by other considerations of equal importance.

A few cases, in which more than one specimen from the same patient was



tested, are shown in Table IV. They are sufficient to demonstrate that no sound prognosis can be made from periodical examinations of the discharge. For of the three cases (E, F, G) which show a distinct fall of the index, one made a rapid recovery, while the other two died.

Moreover, in Case C, in spite of a marked improvement of the index, a fatal result ensued. Case A shows a very slow, but steady rise of index, running more or less parallel to improvement of physical condition.

It seems probable that aggressins may be formed locally in pus which has stagnated for a while within a drainage-tube. The marked increase of aggressin in Case F may be explained in this way.

TABLE IV.

Cases in which the exudate was examined on more than one occasion.

Case.	Date.	Index.	Remarks.
	1913		
A.	E. C.	Feb. 2	Patient was sent to a convalescent home with a discharging sinus on May 2
		Feb. 8	
		Feb. 18	
		Mar. 3	
B.	S. F.	Feb. 15	Recovery took four weeks
		Feb. 17	
		0.7	
C.	E. M.	1 day after operation	Diffuse peritonitis. Improved for a few days, then died
D.	A. G.	2 days	Slow recovery
		April 10	
		April 11	
E.	F. B.	April 29	Died May 21, 1913
F.	C. W.	May 1	Good recovery
		May 6	
		May 8	
G.	C. S.	May 14	Died in seven days
		May 16	

## LIST OF MISCELLANEOUS CASES.

1. Acute salpingitis, clear pelvic effusion, sterile. Index to *B. coli* 0.9. Recovered.
2. Acute salpingitis, clear effusion, sterile. Index to *B. coli* 1.0. Recovered.
3. Double salpingitis and pelvic peritonitis, pneumococcus and *B. coli*. Index 0.1. Died with general peritonitis and pleurisy.
4. Perforated gastric ulcer. General peritonitis. Sterile. Index 1.0. Died.
5. Perforated duodenal ulcer. General peritonitis, streptococcus and pneumococcus. Index to streptococcus 0.6. Died.
6. Clear pleural effusion, sterile. Index 1.1. Recovered.
7. Clear fluid round an appendix-abscess, sterile. Index 0.9. Died.  
N.B.—This is the fatal abscess of Table I.
8. Haemorrhagic pancreatitis. Bloody peritoneal fluid. *B. mucosus capsulatus*. Index 0.5. Died.
9. Bone-abscess. *Staph. aureus*. Index to *Staph. aureus* 0.0 (to *B. coli* 0.5). Recovered.

A list of miscellaneous cases is here given, which includes those that do not come within the scope of the various tables. It calls for little comment, but it is interesting to note that No. 7 is the fatal abscess-case of Table I. As is seen here, the abscess was surrounded with fluid which was sterile and completely

devoid of aggrassin—in fact its opsonic content was more than half that of normal serum—while the pus inside the abscess was powerfully aggressive.

A comparison of the effect of exudates on a normal serum with their action on immune serum (i. e. the serum of the patient) was made on a number of occasions, but no conclusions of any value were arrived at.

The immune serum may possess an opsonic power greater, equal to, or less than that of normal serum, but the first possibility is seldom realized, and the opsonic index is usually low to *B. coli*. A definite relationship of opsonic index and clinical condition was looked for in vain.

Again, the susceptibility of the sera to aggression varied considerably, and though it frequently appeared that the immune serum showed a higher degree of resistance, yet the phenomenon was by no means constant, and might fail in cases whose clinical course suggested a strong recuperative power. Most of the variations in the behaviour of the sera were within the limits of experimental error, which are notoriously wide in opsonic estimations.

For the sake of comparison a few experiments were carried out with a modification of the technique used in estimating the haemophagocytic index of blood.

A small quantity of blood from a pricked finger was drawn into a Wright's capillary pipette and immediately mixed with twice its volume of 0.9 per cent. citrated saline solution. One volume of this mixture was incubated with one volume of exudate in a small test-tube for one hour at 37° C.

At the end of this period a suitable quantity was mixed with bacterial emulsion in a capillary pipette and incubated again for fifteen minutes in the opsonic incubator, and films were made in the usual way.

In each of these experiments normal and immune blood were both employed. The results in the majority of cases were of no value, since the addition of the exudate usually caused clotting of the citrated blood. But there were a few in which no clotting occurred, and the counts showed that it was the aggressive exudates which had lost the power of causing coagulation.

An instance of parallel 'haemophagocytic' and 'opsonic' experiments is given here.

(A)			
<i>Haemophagocytic.</i>	Cells counted.	No. of Bacilli.	Blanks.
(Normal blood + saline) + <i>B. coli</i> citrated . . . .	50	108	15
(Normal blood + exudate) + <i>B. coli</i> citrated . . . .	50	8	43
(Immune blood * + saline) + <i>B. coli</i> citrated . . . .	50	189	13
(Immune blood + exudate) + <i>B. coli</i> citrated . . . .	50	84	23

(B)			
<i>Opsonic.</i>			
(Normal serum + saline) + leucocytes + <i>B. coli</i> . . . .	50	128	8
(Normal serum + exudate) + leucocytes + <i>B. coli</i> . . . .	50	56	27

\* Immune blood = Blood of patient.

N.B.—Brackets denote incubation for 1 hour at 37° C.

It will be seen that a greater degree of aggression (to normal blood) is evident in the haemophagocytic than in the 'opsonic' test; the index in the former being 0.07, while in the latter it is 0.4.

The immune blood shows a greater resistance to aggression than normal blood (indices 0.4:0.07), and this is in agreement with the circumstance that the immune blood by itself shows a higher phagocytic activity than normal blood.

The discrepancy of the indices is more marked in this experiment than in any of the few other parallel estimations carried out. In fact, the agreement of the results obtained by the two methods is as close as it is reasonable to expect.

*Practical considerations.*

The conclusions at which we arrive in considering the experiments tabulated in this paper are as follow:

(1) Any exudate found in the peritoneal cavity in gangrenous or perforative appendicular peritonitis may be aggressive, unless—

(2) It is very recent (24–36 hours), when it is very unlikely to show any aggression, or

(3) It is quite clear and transparent—in which case it is never found to be aggressive.

(4) Thick, offensive pus is nearly always aggressive, and usually to a high degree.

(5) Appendicular abscesses in the vast majority of cases contain markedly aggressive pus.

(6) The presence of a strongly aggressive exudate in the general peritoneal cavity is a great danger to the patient.

Now the treatment of well-formed appendicular abscesses, which is universally adopted, is incision and drainage, and in a large majority of cases this is successful, although the time taken for complete recovery is frequently prolonged.

But we can well make a distinction between cases (1) in which the abscess is adherent to the anterior abdominal wall, and is therefore directly incised, and (2) in which the abscess is opened and drained across the peritoneal cavity. The former class of cases should theoretically respond in an ideal manner to operation, and in practice the results are at least good, and the mortality approximates to zero.

A good deal of interest, however, attaches to the second class of abscesses. My experiments strongly suggest that it is a dangerous proceeding to break through the wall of an abscess containing aggressive pus, and thereby to put its cavity into communication with the general peritoneum. For such a proceeding does not merely open a channel of bacterial infection, which the healthy peritoneum might be expected to resist, but it also admits the escape of a fluid which is capable of paralysing the defences of the cells with which it comes into contact.

Now the practical experience of some surgeons corroborates these experimental deductions. They are convinced of the danger of transperitoneal abscess-drainage, and have adopted alternative methods with great success.

Table I contains the only fatal abscess-case in my series; the cause of death was general peritonitis after transperitoneal drainage of an abscess containing highly aggressive pus.

Widespread or general peritonitis is a very serious condition whatever be the quality of the exudate, though Tables I and III show that if the stage of aggression has been reached before operation, the prognosis is distinctly the worse, and little hope of success can be entertained when an offensive fluid is found everywhere in the belly.

It would seem that the only chance for such cases lies in the removal of the pus, and in bactericidal treatment of its bed. A number of French and German surgeons have recently been treating severe cases of peritonitis with different bactericidal chemicals, and they claim to have achieved a great measure of success.

Pure ether has been used by Souligoux, Morestin, Temoin, and Auvray (11). Souligoux first employed it in a case of acute intestinal obstruction, in which the greatly distended small intestine was ruptured during the operation, with the result that a large quantity of foul intestinal contents flowed into the peritoneal cavity. About a litre of ether was at once poured into the belly and mixed with the faecal fluid. Then the peritoneum was swabbed dry, and completely closed, some 50 c.c. of fresh ether being left inside. Recovery was uneventful, and no late complications ensued. All these surgeons are unanimous in recommending this method, the value of which they have tested on a large number of cases.

When ether is poured into the peritoneum, it is rapidly vaporized and the vapour distends the belly and penetrates all the recesses, where it kills or inhibits the growth of the bacteria.

It is slowly absorbed, and it acts as a continuous stimulant to the heart and respiration. No damage to the serous membrane has been found to result from it.

Another chemical body which seems to be particularly well suited to use in the peritoneum is colloidal silver (collargol, electrargol), for it possesses distinct bactericidal power, and it is tolerated by the body in large doses (7). But perhaps its most striking property is that of stimulating phagocytosis.

Pastia (10), Bossan and Marcelet (2), and Werner (13) have demonstrated not only that the opsonic index in animals is raised after intravenous injections of colloidal silver, but that the addition of a solution to mixtures of serum, phagocytes, and bacteria *in vitro* causes an increase in the numbers of bacteria ingested (1). These experimental results would lead one to expect a very favourable local effect of the preparation upon an inflamed area of peritoneum: (i) by killing bacteria; (ii) by stimulating phagocytosis, and thus acting anti-aggressively. Jelke (6) has used it in several severe cases with highly satisfactory results, and Cr  d   (3) claims that by free use of this substance he

has reduced the mortality in his cases of general peritonitis to a striking extent.

Now considering peritoneal inflammation from the points of view of aggressins, there are at least two types of cases which seem to call for something more than appendicectomy and drainage. Exudates still confined to the region of the appendix but not walled in by adhesions, when they are very turbid, thick, or above all offensive, constitute one type. For in them bacteria are present invariably in enormous numbers, and even a thorough swabbing-out leaves behind many millions of living organisms, sufficient in fact to render aggressive in a short time any fluid which may be poured out into that region. Nor does a drainage-tube constitute a sure safeguard against progressive spreading of the infection. The ideal treatment would evidently aim at destruction of the bacteria or inhibition of their growth, combined with local stimulation of phagocytosis, and it seems that in collargol we have a substance which is admirably suited to these ends.<sup>2</sup>

In Table I there are six cases which come under this description. Of these, two ended fatally; a mortality of 33 per cent.

The second class of cases which evidently requires more than ordinary treatment is the class of diffuse stinking peritoneal effusions. These are often given up by the surgeon as hopeless, and he may do little save the removal of the appendix.

It is indeed hopeless if a large quantity of strongly aggressive and toxic pus is left in the peritoneum, for all defence is in abeyance, and the bacteria continue to multiply until death ensues.

Certainly many of these cases are too far gone to be saved by any means whatever, but some come to operation at a time when there seems to be still hope, if only it were possible to check the rapid formation and absorption of toxic substances.

Appendicectomy and free drainage, though indispensable, are shown by experience to be inadequate, for neither measure puts the break upon bacterial proliferation.

We have seen, however, that in ether and collargol we have two chemical fluids, both possessing at the same time stimulating and antiseptic properties, which could check the growth of organisms, and give the peritoneum a chance of recovery. Moreover, both of them have been given a trial, and have at least in some cases proved equal to the task.

To conclude then, we may say that the study of aggressins in the peritoneum leads us to the conclusion that in the treatment of several varieties of peritonitis, closer attention might with advantage be paid to the question of bacterial multiplication, and to the direct means which are open to the surgeon

<sup>2</sup> Dudgeon and Shattock found that colloidal silver, however administered, failed to prevent the death of animals (mice) which had been injected intraperitoneally with pneumococci. But it must be remembered that this organism produces a rapidly fatal septicaemia which bears no resemblance to the much slower local disorders with which we are dealing.

of checking it. Local chemotherapy by means of drugs which kill or paralyse bacteria without damaging to any considerable degree the living body-cells is not only possible, but has been proved in practice to be at least worthy of a more extensive trial.

Finally, I must acknowledge with gratitude the help and advice given to me by Dr. L. S. Dudgeon in connexion with this research, and the trouble taken by the House Surgeons and House Physicians of St. Thomas's Hospital in obtaining material for me.

TABLE V.

Characteristics of diplo-streptococci from peritoneal exudates.  
22 strains altogether.

Haemolysis . . . . .	positive	2	tested	19
Pathogenicity to mice . . . . .	"	3	"	6
Litmus milk acid and clot . . . . .	"	9	"	22
" " only . . . . .	"	13	"	22
Acidification of dextrose . . . . .	"	18	"	22
" cane sugar . . . . .	"	5	"	22
" lactose . . . . .	"	11	"	22
" raffinose . . . . .	"	1	"	22
" salicin . . . . .	"	3	"	22
" sorbite . . . . .	"	0	"	22
" inulin . . . . .	"	0	"	22
" mannite . . . . .	"	1	"	22

Note.—Six of these strains were tested twice, the second test in each case giving results which differed slightly from the first.

Morphology: various, nearly always diplococcal in original pus. Usually clumping diplococcus on solid media growing into chains of varying length in fluids.

TABLE VI.

Bacteriology of exudates in Tables I, II, III A, and III B. (Aerobic cultures only).

The numbers show how many times the organism indicated on the left was found in conjunction with the one indicated above. Thus both single and mixed infections are shown.

	B. coli.	Streptococcus.	B. muc. caps.	Pneumococcus.	Diphtheroid.	Staph. albus.	B. pyocyaneus.	Coliform b.	B. proteus.	Mixed with more than one other organism.
B. coli . . . . .	8(A)	24	—	—	—	—	—	1	—	—
Streptococcus . . . . .	24	3(B)	2	—	—	1	—	1	—	—
B. mucosus capsulatus . . . . .	—	2	1	—	—	—	—	—	—	—
Pneumococcus . . . . .	—	—	—	1	—	—	—	—	—	—
Diphtheroid B. . . . .	—	—	—	—	1	—	—	—	—	—
Staphylococcus albus . . . . .	—	1	—	—	—	—	—	—	—	—
B. pyocyaneus . . . . .	—	—	—	—	—	—	—	—	—	1 (+ B. coli + streptococcus)
Coliform bacillus, species undetermined . . . . .	1	1	—	—	—	—	—	—	—	1 (+ streptococcus and a coliform bacillus)
B. proteus . . . . .	—	—	—	—	—	—	—	—	—	1 (+ streptococcus and B. coli)

(A) In 6 of these diplococci were seen, but failed to grow.

(B) In one of these bacilli were seen, but failed to grow.



*Summary.*

1. A considerable number of peritoneal exudates have been tested for aggressive action (inhibition of phagocytosis *in vitro*).

2. Aggressiveness is the direct consequence of a profuse multiplication of bacteria. The greater the number of bacteria, the more likely is the fluid to act aggressively.

3. Early exudates therefore (first twenty-four hours) are never aggressive.

4. Aggressive substances are nearly always present in pus from appendicular abscesses, and they do no harm so long as the abscess wall remains intact. But they may play an important and dangerous part when a channel of communication is formed between the abscess cavity and the general peritoneum.

5. In spreading or already diffuse peritonitis, the formation of aggressive bodies, signifying as it does great bacterial activity, marks the onset of a graver stage of the infection.

6. A consideration of aggressins, their origin and their action, suggests that a discriminating use of bactericidal chemicals may be of great value in the surgical treatment of peritonitis. In ether and colloidal silver we have two such bodies which have undergone a successful trial.

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## THE LEUKAEMIAS: AN ANALYSIS OF FIFTY-NINE CONSECUTIVE CASES

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With Plate 26

THIS article is based upon our personal observation of 59 consecutive cases of leukaemia, which are divided into: *Myeloid leukaemia* (i) acute, (ii) chronic; and *Lymphoid leukaemia* (i) acute, (ii) chronic.

### *Acute myeloid leukaemia.*

This is an acute febrile disease characterized by the appearance in the peripheral blood of an immature cell of marrow origin in relative preponderance and in large numbers.

The total number of our cases is 16, of which 2 had the symptoms and signs of chloroma. Of the 16 patients, 5 were Hebrews. The general proportion of Hebrews throughout the London Hospital is 1 to 7. The number in this series is thus above the normal. Eleven of the cases occurred in males and 5 in females. This agrees with the incidence of chronic myeloid leukaemia. The average age of the 16 cases is 22 years. Nine patients, more than half of the total number, were under 15 years of age. The remaining cases show no special age-incidence. The condition is thus commonest in the first two decades of life. The youngest patient was aged 3 years, and the oldest 64 years.

Of possible predisposing causes the following occurred: Two cases had septic teeth; two cases had septic tonsillitis, one of whom also had a foul vaginal discharge; one had cystitis, and one patient dated the onset from an alleged attack of fish-poisoning. None of the conditions occurred so frequently as to suggest a causal relationship.

Before coming under observation the alleged period of ill health varied between 2 days and 6 months, the average being 2 months. While under observation the length of illness varied between 2 days and 11 weeks, the average being 20 days. The total duration varied between 2 weeks and 6½ months. There is no definite relation between the age of the patient and the duration, but in the small number of patients over 40 the duration was very short.

All the patients died of the disease under observation with the exception of one (Case 2), who discharged herself.

*Symptoms.* The onset and symptoms of the condition resemble those of acute lymphoid leukaemia. The patients came under observation complaining of the following: enlarged glands, 4 cases: increasing pallor, 3 cases; increasing weakness, 3 cases; bleeding and swelling of the gums, 3 cases. This list represents the usual nature of the onset. In no case did the size of the spleen attract attention. One patient was brought to the hospital for diarrhoea and lived for some weeks. One woman was admitted for uterine haemorrhage. Constipation is common, but apart from this, gastro-intestinal disturbances are usually confined to the last few days of life.

*Physical signs.* The spleen was enlarged in 12 cases. In 4 cases it extended down to the level of the umbilicus. In 5 cases it was just palpable. In no case was it noticed by the patient, but in one case (No. 10) it was tender to palpation and painful. The lymphatic glands were enlarged in 10 cases. In one case only the cervical glands were palpable, but in all the others the enlargement was general. In some cases they formed obvious masses and in others they were small, but no relation between size and age or duration could be recognized. The liver was enlarged in 10 cases, but only in 2 cases was the size very great.

Haemorrhages occurred in 11 cases. In 5 of these purpura was present, in 6 bleeding from the gums, in 3 epistaxis, in 2 bleeding from the uterus (of a total of 5 females), and in one case haematuria occurred. In 4 of the 5 cases of purpura, bleeding from the gums also occurred. In one case the severity of the uterine haemorrhage led to the patient being brought to hospital, but in general the amount of blood lost by haemorrhage was not very great, except in the group with Rieder cells. In 3 cases neither the spleen, glands, nor liver were palpable, and, apart from an attack of epistaxis, no haemorrhages occurred in this group. Of the 6 cases in which spleen, glands, and liver were all palpable, all had some form of haemorrhage. Of the 11 cases with splenic enlargement all but one had haemorrhages, and of the 4 cases without palpable spleens only one had any form of haemorrhage, this being an attack of epistaxis. Thus purpura and haemorrhages do not appear to occur in acute myeloid leukaemia in the absence of glandular enlargement. These cases without lymphatic and splenic enlargement have leucopenia.

Wasting was recorded in all the cases. No skin tumour was present in any case.

Diarrhoea occurred in 2 cases. Constipation is more usual and was noted eight times. Vomiting occurred in 10 cases, but was almost confined to the last few days of life. Ascites was not present in any case. Oedema of the legs and feet occurred in 2 cases. Some degree of pyrexia was present in every patient. Usually the temperature remained high to the end, but occasionally it fell before death. Retention of urine and suppression of urine each occurred once. One patient had cystitis with frequent micturition. There was no case of priapism.

Intercurrent affections are negligible. Bronchitis was present once, and cystitis once. None of the females were pregnant.

In the 15 cases which died in hospital, no complications occurred, and death may be ascribed directly to the disease.

*Prognosis.* A fatal ending is invariable. The only question which can arise is the probable duration. The longest time under observation in this series was nearly three months. The younger patients lived longer than the older ones. No relation can be traced between the duration and the number of leucocytes. Fourteen of the 16 cases showed myeloblastic leukaemia. When the diagnosis of this has been made, the duration of life does not exceed a few weeks, either in the acute form or when occurring at the termination of chronic myeloid leukaemia.

*Diagnosis.* The definite diagnosis of this condition must rest on the examination of the blood. Suspicion may arise with patients in whom there has occurred a rapidly progressive anaemia and weakness without anything to account for it. In those cases where there is general glandular and splenic enlargement with purpura and haemorrhages, a correct diagnosis of acute leukaemia may be made occasionally before examination of the blood. It must, however, be recollected that none of these physical signs may be present. The diagnosis of this condition is unlikely when purpura and haemorrhages occur without glandular and splenic enlargement.

*The blood-changes.* The examination of the blood (*vide* Table I) divides the 16 cases into three groups according to the predominant leucocyte present:

<i>Group I.</i>	Predominant cell is a myeloblast, includes 10 cases.
<i>Group II.</i>	"          "          large hyaline,    "      4    "
<i>Group III.</i>	"          "          myelocyte       "      2    "

*Group I.* The predominant cell at death was a myeloblast. Schültze in 1906 called attention to the bone-marrow origin of these mononuclear cells, and Pappenheim in 1908 first showed that they were constantly present in the blood in chronic myeloid leukaemia. Morphologically, the nucleus and cytoplasm of the cell differ from that of lymphocytes. The cells vary in size, and there are slight differences between the large and small variety. The nucleus occupies a large proportion of the cell, the cytoplasm forming merely a narrow ring in the small variety of myeloblast. The chromatin structure of the nucleus has a regular, fine, closely-woven appearance, thus differing both from the loose structure of the nucleus of the large lymphocyte and from the irregular gatherings of chromatin in the nucleus of the small lymphocyte. Definite nucleoli, one to four in number, are present in the majority of myeloblasts, more frequently in the large variety. The cytoplasm stains an extremely characteristic greenish blue colour, is frequently vacuolated, and contains no granules.

The size of the cell varies between that of a small and large lymphocyte, but the morphological characters vary little, the cytoplasm being less in amount in the small than in the large variety.

The 10 cases in Group I may be further subdivided for consideration as follows:

- (a) Without glandular enlargement, numbering 2 cases.
- (b) With characteristics of chloroma, „ 2 cases.
- (c) Simple myeloblastic leukaemia, „ 6 cases.

In *sub-group (a)* neither the spleen, glands, nor liver were enlarged. The cases are Nos. 1 and 2. The onset in these patients was insidious and there was nothing in the condition to suggest leukaemia. Case 1 was suspected to have *B. coli* bacilluria, and Case 2 complained of weakness and was admitted on account of the anaemia. In neither was purpura or bleeding from the gums present. The cases further agree in the absence of any marked leucocytosis.

There is no aetiological connexion between these cases. The respective ages were 5 and 64 years. One lived three months under observation. The other patient, Case 2, unfortunately insisted on leaving the hospital after seven days, and has not been traced since. The autopsy in Case 1 revealed nothing. There was no glandular enlargement, no thymus, no haemorrhages and no infiltrations of organs, and there was no oral sepsis. This case is remarkable for its comparative chronicity. The child did not appear very ill on admission and was three months under observation, the total duration of illness being about five months.

*Sub-group (b)* of 2 patients presented the characteristics of chloroma. It is noticeable that the only 2 cases of chloroma which came under observation were myeloblastic and not lymphocytic. The cases showed considerable differences.

In Case 3 on admission there was general enlargement of the lymphatic glands, this having caused the parents to bring the child to hospital. There was no enlargement of spleen or liver, and no purpura or haemorrhage. The temperature was raised. There was a leucopenia, but the differential count showed little abnormality, when the age and general condition of the patient are considered. Small lymphocytes formed 52 per cent. of the white cells. The lymphocytes were all typical. At this time there was nothing to suggest chloroma, but the characteristic symptoms developed rapidly while the predominant cell in the blood altered. Two weeks after admission 50 per cent. of the leucocytes were myeloblasts, while a week later 80 per cent. were myeloblasts, and only 2 per cent. lymphocytes. Comparison of the blood-films of this case at the various dates shows typically the differences between lymphocytes and myeloblasts. This is one of the cases in which the change of the blood to myeloblastic leukaemia occurred while under observation (*vide* Cases 1, 2, 4, and 5, Chronic myeloid leukaemia). Permission for a post-mortem examination was refused.

It may be said that in this case a change occurred from a lymphocytic to a myeloblastic leukaemia. If this is so, it is unique in the present series, although occasional myeloblasts are found in the blood in lymphatic leukaemia. There was, however, on admission nothing in the blood-film to suggest a diagnosis of lymphoid leukaemia.

In Case 4 on admission the spleen reached to the level of the umbilicus, there was general glandular enlargement and the liver was palpable. There was purpura, bleeding from the gums, and epistaxis. The blood examination showed 150,000 leucocytes with 99.5 per cent. myeloblasts. The blood remained unchanged. The characteristics of chloroma—that is to say, marked proptosis and subperiosteal infiltrations about the base of the skull—developed whilst the patient was in hospital. He lived seven weeks under observation.

The physical signs and blood-changes in this patient thus differ widely from Case 3. The general condition resembles that of several cases classed as 'simple myeloblastic leukaemia', while Case 3 resembles the cases without glandular enlargement.

The post-mortem examination showed general glandular enlargement with a large haemorrhagic thymus, cellular infiltration of the left temporal and masseter muscles and of the dura and left kidney, necrosed infiltrations in the sphenoidal and ethmoidal sinus, and a large deposit in the medulla of the right humerus. There was gelatinous red marrow in the humerus, femora, ribs, sternum, vertebrae, and calvarium. No green colour was noticeable. There were petechiae in the serous membranes.

In *sub-group (c)* six cases (Nos. 5 to 10) are classified as 'simple myeloblastic leukaemia'. They showed marked glandular enlargement, and in four cases the spleen was enlarged to the level of the umbilicus. Purpura was present in 3 cases, but profuse haemorrhage occurred in only one case, this following the extraction of teeth. The total duration was short, the longest period being 8 weeks, and the average 4 weeks, while the average for the 16 cases of acute myeloid leukaemia is 9 weeks. Four of the six were Hebrews. In all cases the blood-changes were fully developed on admission, the lowest percentage of myeloblasts being 74 per cent. The blood showed little change while under observation. The number of leucocytes varied greatly in the different cases. In 2 cases there was leucopenia. The leucopenia did not correspond with any definite clinical symptom or sign.

In Case 5 a sample of blood was mixed with a suspension of *Staphylococcus aureus*, in order to ascertain whether the myeloblasts had any phagocytic action. One myeloblast in many thousands contained 4 cocci, the remainder being empty. Evidently the myeloblast is non-phagocytic. On the day preceding death marked lipaemia was present. The amount of fat was so great that it was impossible to obtain a satisfactory blood-film. The cells separated rapidly, leaving an opaque white serum, the free fat globules staining readily with Scharlach. The oxydase reaction showed no granules in the cells of this case. Permission for a post-mortem was refused.

Case 6 came under observation owing to severe haemorrhage following the removal of carious teeth. This was the only case where there was any oral sepsis.

In Case 7 the oxydase reaction was also negative. The blood showed a leucopenia. Post-mortem examination showed a persistent thymus and general glandular enlargement. There were haemorrhages in the stomach, kidney, and knee-joint. There was pink-grey marrow throughout the femur and vertebrae.

Case 8 was admitted to hospital in a state of collapse. The previous history



of ill health was less than three weeks, and the patient was obviously moribund. Post-mortem examination showed enlargement of the internal lymphatic glands, and haemorrhages into the serous sacs and left internal capsule. The cervical glands had a definite green colour, and there was greenish marrow in the upper half of the femur and in the humerus.

Case 9 was brought to hospital for purpura and bleeding from the gums. It is the only case of acute myeloid leukaemia in which leucopenia was associated with purpura, this being very profuse.

Case 10 was admitted for general weakness. He complained of pain in the left hypochondrium. The spleen reached to the groin but was not tender to palpation.

Post-mortem examinations were performed only on Cases 6 and 7, the remaining four being Hebrews.

The blood picture in these 6 cases resembles the terminal myeloblastic stage in Cases 1, 2, 4, and 5 of the series of chronic myeloid leukaemia. In 4 of these 6 the spleen reached to the level of the umbilicus, so large a size not being found in any of the remaining 10 cases of acute myeloid leukaemia. It is possible that this series of simple myeloblastic leukaemia represent the terminal stages of previously unrecognized cases of chronic myeloid leukaemia. One might equally advance the theory that acute lymphoid leukaemia is the terminal stage of the chronic disease. There is no obvious method of either proving or disproving these possibilities.

*Group II.* The predominant cell in this group resembles most nearly the large hyaline of normal blood (Rieder cell). A short description is given of these cases:

*Case 11.* L. C., aged 36 years, married. Admitted April 24, 1909. She was taken ill with 'influenza' two months before admission and had not been well since. There had been a septic mouth, a foul vaginal discharge, and progressive anaemia. Until shortly before admission there had been no purpura or haemorrhage, but bleeding from the uterus then occurred and led to her coming to the hospital. On admission there was advanced anaemia, oral sepsis, and uterine haemorrhage. The spleen and liver were palpable, but there were no enlarged glands. The patient died on April 28. The blood showed 228,000 leucocytes, of which 74 per cent. were classified as large hyalines. A few myeloblasts and myelocytes were present. There was advanced secondary anaemia, but no nucleated red cells.

Post-mortem examination showed some enlargement of lymphatic glands, haemorrhages into the pericardium and uterus, and infiltration of the liver and kidneys. There was grey marrow in the sternum, vertebrae, ribs, and upper half of femur and 'red-currant jelly' marrow in the lower half of femur.

*Case 12.* L. A., aged 12 years. Admitted November 20, 1911. He had not been well since an attack of diarrhoea in August, 1911. In September the cervical glands were found to be enlarged and the gums became swollen. There had been no haemorrhages. The swelling of the gums became extreme and caused the patient to be brought to hospital.

On admission there was general enlargement of the glands, the spleen was palpable and the liver enlarged. The gums were swollen but the teeth were good,

and there was no haemorrhage or purpura. The spleen increased in size and haematuria occurred and also bleeding from the ears and gums. The patient died on December 14.

The blood-count on admission showed 160,000 leucocytes, of which 79 per cent. were classified as large hyalines. Myeloblasts and myelocytes were also present, as well as intermediate forms. Anaemia was present, but nucleated red cells were very scanty. Blood platelets were completely absent on each occasion. The blood underwent no marked change.

*Post-mortem.* There was general glandular enlargement, haemorrhages into the kidneys, testicles, and stomach, and infiltrations in the kidneys. The marrow in the humerus and femur was examined and was soft and greyish red.

*Case 13.* E. D., aged 10 years. Admitted October 6, 1912. The parents thought that the boy had been getting weaker for six months. The feet were swollen in August. In September the glands became enlarged and there was epistaxis. On admission there was anaemia, slight general enlargement of the glands, a palpable spleen, and enlarged liver. There was no oral sepsis, purpura, or swelling of the gums. Profuse epistaxis recurred and the anaemia became extreme. The patient appeared constantly on the point of death, but lived until November 19. The blood examination showed 20,000 leucocytes; of these 32 per cent. were classified as large hyalines. Myeloblasts numbered 45 per cent. Intermediate forms between these cells were present. The myeloblasts were non-phagocytic as in Case 5, but the large hyaline cells were phagocytic. There was advanced anaemia with a high colour index, but the red cells were well formed and nucleated cells very rare. The blood changed very little during observation.

*Post-mortem.* There was general glandular enlargement and haemorrhages into the kidneys. In the humerus and femur there was red marrow.

*Case 14.* E. V., aged 43 years. Admitted January 24, 1913. She was quite well until two months previously. From that time there had been severe haemorrhage from the uterus.

On admission there was extreme anaemia. The spleen and liver were palpable, but the lymphatic glands were not enlarged. There was no oral sepsis, no purpura, and no swelling of the gums. The uterine haemorrhage continued and the patient died on January 27.

The blood contained 48,000 leucocytes, of which 62 per cent. were large hyalines and 13 per cent. myeloblasts. Myelocytes were also present. There was extreme anaemia, but nucleated cells were scanty.

*Post-mortem.* There was enlargement of the internal lymphatic glands and these had a green tint. The marrow examined in the femur and humerus had also a greenish colour.

The predominant cell in these cases resembles, and often is indistinguishable from, the large hyaline of normal blood. The typical cells have a partite nucleus and a feebly basophilic cytoplasm which is often granular. They are sometimes called Rieder cells. In these cases typical myeloblasts are also present in varying percentages, which in Case 13 was as high as 45 per cent. on one occasion. In some cases every intermediate stage can be traced between the myeloblast and the large hyaline in the same blood-film, and also between the myeloblast and myelocyte.

The stages pass through a typical myeloblast, a cell with the nucleus of a large hyaline and a myeloblastic cytoplasm, a granular large hyaline to a large hyaline without granules. There are numerous intermediate steps. Cells

intermediate between large hyalines and polynuclear neutrophils were also present in some films. For these reasons we consider that these large hyalines are cells of bone-marrow origin and derived from the myeloblasts, but are more mature. Further, the myeloblast is a non-phagocytic cell, but in the one case examined the large hyalines were found to be phagocytic.

Clinically these cases of hyaline leukaemia are not unlike those of myeloblastic leukaemia. They are very acute. There is general glandular enlargement. The condition is well established when the case comes under observation, and the blood subsequently changes but little.

On the other hand, in this group, which we may call 'acute hyaline leukaemia', there was no case of purpura, although severe haemorrhage occurred in each patient. Thus both the females came under observation for bleeding from the uterus. This contrasts with the cases of simple myeloblastic leukaemia in which purpura was common, but profuse haemorrhage rare. In each case the number of leucocytes was high. None of the four patients were Hebrews.

*Group III.* The two cases of this group differ from the remaining cases of acute myeloid leukaemia since myeloblasts do not form the predominant feature of the blood.

*Case 15.* P. T., aged 37 years. This patient was admitted for cystitis, the dysuria having existed for a period of possibly six months. On admission the extreme anaemia was noticed and the blood examined. There was no enlargement of glands, liver, or spleen; no purpura or haemorrhages, and no oral sepsis. He died four days after admission. Examination of the blood showed marked leucopenia. Mast-cells formed 12 per cent. of the leucocytes, and myeloblasts about the same proportion. Myelocytes of all varieties formed 18 per cent., the most striking feature in the blood being 9 per cent. of amphophilic myelocytes, containing both basophilic and eosinophilic coarse granules. In no other case has so high a percentage of these cells been present. In spite of the extreme anaemia the red cells were almost normal in character. Rouleaux formation was normal; there was practically no poikilocytosis and no nucleated red cells. The differential count resembles most closely a myelocytic leukaemia.

Post-mortem examination showed no abnormality except that the marrow had a greenish tint.

*Case 16.* E. P., aged 22 years. The patient complained of feeling tired. The duration of ill health was doubtful, but did not exceed six months. On admission anaemia was advanced. There was slight general glandular enlargement and the spleen was palpable. There was no oral sepsis. The blood contained 30,000 leucocytes, of which 20 per cent. were myelocytes. No myeloblasts were present. Mast-cells were scanty. The changes in the red cells were extreme, the number of nucleated cells, especially megaloblasts, being very large and poikilocytosis and polychromatophilia marked.

While under observation the leucocytes increased in number, and in the last count before death 60 per cent. were neutrophilic myelocytes. Purpura and bleeding from the gums occurred. The changes in the red cells increased, the anaemia becoming extreme, and nucleated red cells were almost as numerous as the leucocytes. The patient died after two weeks, apparently from the changes in the red cells.

Post-mortem examination showed general glandular enlargement and a persistent thymus. There was no infiltration. The marrow examined was red.

This appears to have been a case of acute myelocytic leukaemia with extreme changes in the red cells.

In all cases a marked diminution both of the red cells and haemoglobin was present when the patient came under observation. The anaemia advanced with the disease and often became extreme. The colour index is distinctly higher than is commonly observed in secondary anaemia of a severe type. Nucleated red cells, both normoblasts and megaloblasts, were present in the majority of cases, but only in Case 16 did they form a prominent feature. In Case 10 a few gigantoblasts were repeatedly present, but no normoblasts.

*Post-mortem examinations.* The following is a summary of the changes in 10 cases in which a post-mortem was allowed. Permission was refused in 4 of the 6 cases of simple myeloblastic leukaemia.

Lymphatic glands were enlarged in 8 cases. In one case they were green (Case 14). There was no green tint in either case of chloroma. The enlargement was general. The thymus was persistent in 3 cases, Nos. 4, 7, and 16. The spleen was enlarged in 9 cases. The largest spleen weighed 3 lb. 14 oz. The bone marrow was altered in all cases. In three cases there was a greenish tint, but this was not present in either case of chloroma. The marrow was variously described as 'red', 'grey-red', 'grey', and 'pink-grey'. Haemorrhages were present in 9 cases. In 3 cases there were haemorrhages into the stomach, and in 3 into the glands. Other sites affected were the kidneys, omentum, gums, testicles, internal capsule, and fundus. Infarcts were absent in all cases. Infiltration was present in 7 cases. The sites affected were the liver, glands, kidneys, and tonsils, Peyer's patches, and root of mesentery. The heart was obviously fatty in 5 cases.

*The oxydase reaction.* This reaction has been advocated as a method of distinguishing between cells of marrow and cells of lymphoid origin. In the normal blood a marked granular reaction is obtained by this means in the cytoplasm of the polynuclear neutrophil and eosinophil cells, and no granules are seen in the small and large lymphocytes. It has been claimed that the primitive marrow-cells which contain no granules staining by the ordinary dyes can be demonstrated to be granular by the oxydase reaction. In addition to a considerable number of normal blood-films we have tested four cases of acute myeloid and two cases of chronic lymphoid leukaemia. Both the myeloblasts and the lymphocytes were non-granular.

The hyaline cell of normal blood is usually non-granular to Leishman's stain, but is occasionally granular. It reacts in the same way to the oxydase reaction. So far as we have been able to determine, those cells which do not show granules by Leishman's stain are negative to the oxydase reaction. We have obtained no assistance from this reaction in distinguishing the primitive marrow-cell from the lymphocyte. On the other hand, these cells can readily be distinguished by Leishman's method of staining.

We may add that in blood-films more than two months old, whether normal

or abnormal, we have failed to obtain any results at all with the oxydase reaction.

*Chronic Myeloid Leukaemia.*

This is a chronic disease of about two years' duration, occurring mainly in young adults, and associated with splenic enlargement and a characteristic blood picture. The total number of cases observed was 29.

Of the 29 patients 3 only were Hebrews, numbers which do not suggest any predisposition of the Jews to this disease. Eighteen were males and 11 females. The ages at which the disease was diagnosed ranged from 8 to 66 years. The average age of incidence was 27.6 years. No history of any previous illness which could have any bearing upon the condition was elicited. Six of the cases had definitely carious teeth, not an undue proportion in patients of the hospital class. Two cases only had been infected with syphilis.

*Symptoms.* The symptoms were almost invariably slight and referable to the discomfort produced by the splenic enlargement. Thus in 22 cases the main complaint was either enlargement of the 'stomach' or a swelling in the 'stomach'. In 4 cases the main complaint was weakness, and in 2 cases only was there a history of pain in the region of the spleen. One case was discovered by chance.

*Physical signs.* The spleen was enlarged in all cases, and in the great majority the enlargement was very considerable. The position of the lower pole varied from two fingers' breadth below the left costal margin to the level of the pubic crest. There was some tenderness on palpation in 2 cases, and splenic pain was complained of in 4 cases.

Glandular enlargement to physical examination was absent in 21 cases. In 3 cases the axillary and inguinal glands were enlarged, in 2 cases the axillary glands only, and in one case the axillary, inguinal, and cervical glands.

In 14 cases, or in nearly 50 per cent., there was definite enlargement of the liver, and the enlargement was particularly constant in the later periods of the disease. There were no skin tumours in any case. Purpura was never present during the ordinary course of the disease. In one of the cases, a child, in which the disease terminated by a condition of acute myeloid leukaemia, purpura was present shortly before death. It is possible that some other cases, who were not under observation at the time of death, developed similar haemorrhagic conditions. Haemorrhage was present in 6 cases, and was usually from the nose or gums. Retinal haemorrhages were noted in some cases, but were not examined for as a routine. They seem to be very constantly present, at any rate when the disease is well advanced.

Clinical 'anaemia' was noted in 21 cases and, as shown by blood examinations, a diminution in red cells or haemoglobin was constantly present. In the earlier periods of the disease, however, anaemia is rarely a noticeable feature. In 20 cases loss of weight was complained of, and in some cases the wasting



was progressive and extreme. Oedema of the legs and feet was present in 11 cases. Ascites was noted in 4 cases.

Pyrexia, usually of an intermittent type and often not of great degree, was very constantly noted. It was observed in 21 cases and was possibly present at some period in all. Many of the cases were only under observation in hospital for short periods.

Gastric disturbances were usually slight, and though vomiting was present in 5 cases it was probably incited by the administration of arsenic. Constipation, diarrhoea, and disturbances of micturition were practically absent. Priapism was not noted in any case.

Death resulted from the disease in all cases, but in one case tuberculous peritonitis was also present. One case developed pericarditis, from which she recovered to die about six months later. One case has passed safely through two pregnancies and is still alive, and in her case the disease certainly seemed to retrogress during each pregnancy.

*The blood-changes.* In all cases the blood at some period of the disease showed the changes typical of chronic myeloid leukaemia. Tables II, III, and IV give the blood-counts made when each patient was first seen, when last examined, and at some interval period.

The points in the blood examination, to which we draw attention here, are the following: (1) The presence or absence of any marked change in the blood as the result of treatment. (2) The occurrence of a myeloblastic change. (3) The occurrence of an erythroblastic change.

1. *The effect of treatment.* The treatment considered here is either the administration of arsenic or the application of X-rays. With one exception all the cases received this treatment. Thus arsenic was given in 25 cases, salvarsan in 4 cases, and X-rays in 22 cases. In a high percentage of cases arsenical and X-ray treatment was combined. Such changes as occurred in the blood were not necessarily the result of this treatment, but there can be no doubt that the treatment was the most important factor in producing them.

The one untreated case discharged himself and has been lost sight of. In another case only one examination was made. There remain 27 treated cases. Of these 27 cases 14 responded to treatment, 13 showed little or no alteration in the blood.

Of the 14 who responded to treatment 7 showed marked blood-changes, and 7 fluctuated to a less degree. By marked changes is meant the appearance either of a leucopenia or an excess of myeloblasts or both. By less-marked changes is meant a diminution in the number of white cells to about 20,000 to the c.mm., but without any myeloblastic change.

Of the 14 cases which responded to treatment 13 had both arsenic and X-rays. Of the 13 cases which did not respond 4 had no X-rays.

Owing to the difficulty of fixing the time of onset of the disease, it is not possible to say definitely which cases ran the longest courses. In only one case, however, in which marked response to treatment occurred, did the known



duration of the disease exceed two years. In 4 of the cases which did not respond, the duration exceeded two years, and in one instance five years. In 5 out of the 7 cases in which response to treatment was comparatively slight, the duration exceeded two years. There can be little doubt that those cases which responded little, or not at all, to the action of arsenic and X-rays lived longer than the cases whose blood readily reacted to treatment, and if this be the case we might be led to the conclusion that the treatment is either useless or positively detrimental. However, an analysis of the cases reveals an additional factor in determining the course of the disease, the factor of age. The average age of incidence was 27.6 years. Of the 13 cases which did not respond to treatment 11 were 40 or upwards, one was 30, and only one less than 20. Of the 7 cases who responded slightly, all, with one exception, were over 30, and the 2 cases which responded least were over 50 and lived the longest. Of the 7 cases which responded readily to treatment 4 were less than 20, and the oldest was 34. The only case, less than 20 years old, who did not respond to treatment was a boy of 18, and he is still alive after  $2\frac{1}{2}$  years.

We conclude, then, that patients of less years than the average age of incidence respond more readily to the action of arsenic and X-rays, as evidenced by fluctuations in the number and character of the leucocytes and to a less extent in the size of the spleen, and that the disease tends to run a more acute course in the younger than in the older patients.

2. *The occurrence of a myeloblastic change.* The cell known as the myeloblast is now well recognized, and we need only repeat here that it is the mother-cell of the myeloid blood-cells, and that it is present in small numbers in all cases of chronic myeloid leukaemia. In a large number of blood-films in this series all the intermediate stages in the transition of myeloblast to granular myelocyte, and of myelocyte to polynuclear leucocyte, can be traced.

The appearance of a marked myeloblastic change is definite evidence of death within a few days, or at most weeks. Since a number of these cases were not examined at the time of death, it is impossible to say how often the change occurs. A marked myeloblastic change occurred in 4 of these cases only, and in 2 of them it was very marked. In a considerably larger number of cases we can certainly say that the change did not occur, but in a few of the older patients a percentage of more than five myeloblasts was present on numerous occasions. Of the 4 cases in which a marked myeloblastic change occurred, one was 30 years of age, the others less than 20. The myeloblast percentage was about 40 in two cases, over 60 in one case, and 98 in another case. In the last case, a Hebrew boy aged 8, the type of cell was remarkable. It was a small cell, almost entirely nucleus, with a narrow rim of purplish staining cytoplasm. A few granules could be seen in some cells. This type of cell is probably more mature than the larger and more frequently met with myeloblast.

The myeloblastic change appears as a rule to develop suddenly, but it may be preceded at a definite interval by marked general disturbances, such as

pyrexia, and in one case purpura, and by a leucopenia. The total number of leucocytes present during the myeloblastic period is rarely high, as might be expected in a condition which is evidently that of marrow exhaustion.

3. *The occurrence of an erythroblastic change.* Some change in the red cells and haemoglobin percentage was present in all cases. The anaemia was nearly always of the secondary type, but in 2 cases a colour index of 1 was obtained and the index was exceptionally less than 0.7, which we should consider a high index in cases of secondary anaemia from other causes. Nucleated red cells, both normoblasts and megaloblasts, were nearly always present; their number was not necessarily high in the more rapid fatal cases.

Decrease in the number of the red cells and in the percentage of haemoglobin was constant as the disease progressed, and could be taken as a fair index of the clinical condition of the patient.

*Diagnosis.* This is rarely difficult provided an examination of the blood be made in all cases of considerable splenic enlargement. The only difficulty that could arise is the possible examination of a patient for the first time after treatment, and at a period when leucocytosis is absent and the spleen little, if at all, enlarged. The spleen, however, may be very large, and at a time when the blood-count is almost normal. Such cases, however, if treatment be suspended, rapidly revert to a condition typical of the disease. We are not conscious of ever having met with this difficulty in practice.

*Duration.* Since it is impossible to say when the disease commenced, particularly in the hospital class of patient, and since some of these cases are still alive or have been lost sight of, the definite duration cannot be given.

Of the 29 patients 18 are dead, 6 alive, and 5 cannot be traced.

The average length of history given on admission was 13 months, the average life under observation was one year. The probable average duration of the disease is from two to three years.

*Prognosis.* Recovery in our experience never occurs, and the longest period we have had a case under observation is four years. The younger patients live a shorter time than those over the age of 40. Great fluctuations in the number of leucocytes are of bad prognosis. The degree of erythroblastic failure is a guide to the progress of the disease. A leucoblastic failure as evidenced by the increase of myeloblasts is certain evidence of rapidly approaching death.

Treatment has been considered under the changes which occur in the blood. Generally, the effect of X-rays appears to be similar to that of arsenic, but on the whole more powerful and more dangerous. Treatment should certainly be suspended if rapid diminution in the leucocytes occurs, and always when the leucocytes approach the normal number. Salvarsan was tried in 4 of these cases, but without any satisfactory result. The more recent drugs, mesothorium and benzene, were not tried in any case.

*Post-mortem examinations.* Post-mortem examinations were made in 8 cases. The spleen was enlarged in all cases and necrotic areas were present

in 2. The lymph glands were enlarged in all cases, and in 2 they were of the green colour associated with chloroma. There was no other unusual feature in these 2 cases, and it is worthy of note that the green coloration may be present in ordinary cases of chronic myelaemia and absent in chloroma. The marrow was red or greyish-pink throughout femur, humerus, and sternum. The heart showed fatty change to the naked eye in one case only. Cellular infiltrations were present in the liver, kidneys, and glands in 3 cases to a degree evident to the naked eye. No haemorrhages were present in any case and no infarcts.

#### *Acute Lymphoid Leukaemia.*

This is an acute febrile disease characterized by the presence in the peripheral blood of a cell morphologically resembling the small lymphocyte in relative preponderance. The number of cases in this group is 8.<sup>1</sup>

Of the 8 patients, 2 were Hebrews. This proportion is the same as in acute myeloid leukaemia. The general proportion of Hebrews throughout the London Hospital is 1 to 7. Seven of the cases occurred in males, and only one in a female. Six of the 8 patients were under 21 years of age. Four were between the ages of 15 and 21 years. The extremes of age were 3 years and 48 years.

Three of the 8 patients had septic teeth. One of these also had enlarged tonsils and otorrhoea. In one other case otorrhoea was present, and in one enlarged tonsils and adenoids.

Before coming under observation the alleged period of ill health varied between 3 weeks and 3 months, the average being 6 weeks. While under observation the duration of illness was between 2 days and 11 weeks, the average being 24 days. The total duration varied between 3 weeks and 3½ months, the average being 9 weeks. There is no relation between age and duration in this group.

*Symptoms.* In all these cases increasing pallor had occurred. Apart from this, various symptoms were present, including weakness, haemorrhage from the gums, purpura, and pain in the chest. One patient, with ascites, complained of abdominal pain.

*Physical signs.* The spleen was enlarged in 6 cases. In 4 cases it extended below the umbilicus. In the other 2 patients, both children, it reached one inch below the costal margin. In no case had the size of the spleen attracted the patient's attention. In one case the spleen was tender to palpation. The lymphatic glands were enlarged in 5 cases. The enlargement was general, but in no case were the glands very large. The liver was enlarged in 5 cases.

Haemorrhages occurred in 6 cases. In 5 of these purpura was present, in 4 bleeding from the gums, in one profuse epistaxis, and in one haematemesis

<sup>1</sup> We have not had the opportunity of re-examining, for the purpose of this article, blood-films from Cases 1 to 4 of this series. The possibility cannot be excluded that the cells in these cases were myeloblasts.

and the passage of blood per rectum. In the two latter cases the amount of blood lost was large. Purpura was always associated with some other form of haemorrhage. In 5 cases the spleen and glands were both enlarged, and in all of these purpura and other haemorrhages occurred. In the remaining 3 patients there was no case of purpura. Thus it appears that in acute lymphoid leukaemia, as in acute myeloid leukaemia, purpura is associated with enlargement of both spleen and lymphatic glands. In 2 cases neither glands, spleen, nor liver were enlarged.

Pyrexia was present in 7 cases. In one the temperature was subnormal. Wasting and pallor were present in every case.

Gastro-intestinal system. Diarrhoea and constipation each occurred twice. Vomiting was present in 6 patients.

Frequency of micturition and polyuria occurred in 3 cases. The urine contained no glucose, there was no cystitis or any apparent cause for the polyuria. In only one of these three (Case 1) was a post-mortem examination permitted, and in this case there were infarcts in the kidneys and also in the spleen. This was the only instance in which infarcts were present. There was no case of priapism, of skin tumour, or of pain in the long bones. Oedema of the feet was present once. In one case there was ascites, together with pericardial and pleural effusions.

Intercurrent affections are negligible. In one case there was slight bronchitis. The only female patient was 48 years of age, and was not pregnant.

All the patients died directly from the disease. In one case death followed profuse haemorrhage.

*Prognosis.* As all patients in this group die of the disease in the course of a few weeks, the prognosis in lymphoid leukaemia is resolved into the diagnosis between the acute and chronic varieties.

Arsenic was used in 3 cases, being tried by the mouth and by injection. Neither the use of this nor the application of X-rays had any obvious influence.

*The blood-changes.* Table V gives the main details of the examinations of the blood. The short duration of the illness resulted in only one single examination being made in some patients. In no case was the predominant cell a typical large lymphocyte. The distinction was made easy in nearly every case by the presence of occasional large lymphocytes. Attention has been called to this point in the description of the blood in chronic lymphoid leukaemia. The predominant small lymphocyte in lymphoid leukaemia frequently has a notched nucleus, but the arrangement of the chromatin and the staining reactions are otherwise normal.

In 4 of the cases myelocytes were present to a small percentage, and occasionally typical myeloblasts were seen. In 2 of these patients nucleated red cells were present in considerable numbers.

In 6 of the 8 cases, the number of leucocytes in the first examination was less than 10,000, that is to say, it was within normal limits. The contrast between the number in this group and in acute myeloid leukaemia is very definite. The average number in the latter group of 15 cases is 66,000 and in the former 22,000,

this figure being greatly influenced by one case. In 2 cases, Case 5 and Case 6, a distinct leucopenia was present. These cases both lived for several weeks after admission and may be described more fully as illustrating the changes which may occur in the leucocytes. In Case 6 tonsillectomy was performed for enlarged tonsils and otorrhoea. A few days later the patient became very ill. On admission there was pyrexia, purpura, haemorrhages from the gums, enlarged liver and spleen, and palpable glands. The leucocytes numbered 2,800, of which 60 per cent. were small lymphocytes. Ten days later the lymphocytes had fallen to 26 per cent., the total count of leucocytes being 5,000. At that time the white cells were practically normal. A month later the percentage of lymphocytes rose to 90, the total counting being 38,500. It remained at this figure for a few days, and then the leucocytes fell to 4,400 the day before death.

Case 5 was admitted for profuse purpura. The liver, spleen, and glands were enlarged. There was no haemorrhage from the gums. The number of leucocytes, in repeated counts, never exceeded 6,000 until they rose to 18,000 just before death. The lymphocytes fell gradually to 60 per cent., and then rose rapidly to over 90 per cent. In both these patients the predominant cell was a typical small lymphocyte. These cases are examples of the frequency of leukopenia and the fluctuations in the differential count which may temporarily fall within the normal limits. In nearly all cases of acute mononuclear leukaemia with high leucocytic count, the predominant cell is a myeloblast and not a lymphocyte.

The anaemia is very severe in this group. The highest percentage of haemoglobin on coming under observation was 35, although slightly higher figures occurred occasionally whilst in hospital. The average is 25 per cent. Before death the percentage fell much lower. The average of the red cells in 6 cases is 1,475,000. It will be noticed that the colour index is high throughout the series, especially when the degree of anaemia is considered. Cases with the leucocytic changes of lymphoid leukaemia and the red-cell changes of pernicious anaemia have sometimes been classified under the name 'leukanaemia'. It will be seen that a high colour index is the rule and not the exception.

The diagnosis of leukanaemia would be applied by some authorities to certain cases in the group, reducing the residue of cases of acute lymphoid leukaemia to a very small figure.

Nucleated red cells may occur, these being usually normoblasts. Megaloblasts are not common. In Case 7 the nucleated red cells were very numerous, the anaemia was extreme.

Acute lymphoid leukaemia occurred less frequently than myeloblastic leukaemia.

*Post-mortem examination.* This was made in 6 cases. Special points may be referred to in 2 cases. In Case 1 the thymus was enlarged and full of cysts. Infarcts were present in kidneys and spleen. There was early haemorrhagic pachymeningitis. Pleural, pericardial, and peritoneal effusions were present. The marrow was red.



In Case 3 there was a mass of infiltration in the caecum, which was oedematous and sloughing. Large nodules were frequent in the rectum. A fine creamy infiltration of glands was present. Pink-grey matter invaded the humerus, femur, and sternum, and there was a very slight rarefaction in the humerus and femur.

The following is a summary of the changes in 6 cases: There was general enlargement of the lymphatic glands in 5 cases. The glands were discrete, hyperaemic, and infiltrated. The tonsils, lingual and faucial, were enlarged in these cases. In no case was a green colour present. The thymus was enlarged in one case. The spleen was enlarged in all cases; in 3 the increase was great. The liver was fatty in all cases. In 4 cases it gave the reaction for free iron. The bone marrow was altered in all cases. The marrow was described as red. In no case was there a green tint. In 3 cases there was rarefaction of bone. Haemorrhages were present in all cases. The lymphatic glands, spleen, pericardium, and pleura were mainly affected. Infiltrations were present in 5 cases, the liver, glands, and kidneys being affected. The heart was fatty in 3 cases.

#### *Chronic Lymphoid Leukaemia.*

This is a chronic disease of a year or more duration, occurring in adult life, and associated with enlargement of the spleen and lymph glands and a marked relative and absolute increase in the lymphocytes of the circulating blood. The total number of cases described is 6.

Of the 6 cases, 2 were Hebrews, a number considerably above the proportion of Jewish patients to those of other nationalities in the London Hospital. Four were males and 2 were females. The ages of the patients varied from 40 years to 69 years. The average age was 54.

In no case was there a previous history of any illness of importance. In 2 cases the teeth were sound. In the remaining cases there was no notable evidence of oral sepsis.

*Symptoms.* The main symptoms complained of on admission were mainly of a special character referable to the size of the glands or the spleen, and to the discomfort produced by the enlargement of these organs. Thus, two complained of abdominal discomfort, one of swelling of the neck and dyspnoea, one of a swelling and pain in the left side, and two of loss of weight and weakness.

*Physical signs.* The spleen was enlarged in all 6 cases, and the enlargement was almost as great as that met with in chronic myeloid leukaemia. The position of the lower pole of the spleen varied from the level of the umbilicus to the neighbourhood of the pubic crest.

The enlargement of the lymphatic glands was in the great majority of cases a relatively inconspicuous feature. In 2 cases no glandular enlargement could be detected. In 4 cases palpable glands were present in the groin and axilla or in the groin and the neck. In only one case could the glandular enlargement be



described as a conspicuous physical sign. In this case there was great enlargement of the neck glands, and clinical evidence of considerable enlargement of the mediastinal glands also.

The liver was palpable in 2 cases only. In one of these cases a frank history of alcoholic excess was given, and the patient had the appearance and the marked icteric tinge associated with a cirrhotic liver. No leucocytic infiltrations of the skin were present in any case.

Purpura and haemorrhage were absent in all cases. Pallor was noticeable in one case only, and then only a few weeks before death. Obvious anaemia was absent during the earlier periods of the disease.

Loss of weight, noticeable to the patient, was recorded in 4 cases.

Fever. In 2 cases some pyrexia was present, but in one of these patients the pyrexia was temporary and apparently unconnected with the disease. The other febrile case died three months later. The remaining cases were afebrile while under observation. The functions of the alimentary and genito-urinary systems were normal in all cases.

There have been no intercurrent affections of any significance. One case is mentally unstable, and another case, which has been under observation for about five years, is now in extremely poor health, and this condition appears to be due rather to alcoholic cirrhosis of the liver than to the blood state.

Only 2 cases are dead, and so far as could be ascertained there were no intercurrent affections.

*The blood examinations.* Table VI gives an abbreviated description of the blood examinations. The first and last counts made are given, together with one count taken at an intermediate time.

The main feature of the blood in all cases is the great predominance in the number of lymphocytes. In 4 cases the lymphocytes were of the small variety, and in 2 cases of the large variety. On the whole, the 2 cases with the large lymphocytic predominance appeared to be less profoundly affected than the remaining 4 cases, of which 2 are dead, but we are not justified in drawing any definite conclusion upon this point. The statement is generally made that cases of lymphoid leukaemia in which the small lymphocytes are predominant tend to run a chronic course, whereas the large lymphocyte variety tends to a rapidly fatal termination. This statement is quite unjustified, and has probably been made partly from a confusion between lymphocytes and myeloblasts, partly from an inability to distinguish between the small and large lymphocytes. The lymphocytes almost invariably met with in both acute and chronic lymphæmia are of the small variety, but they are frequently larger than the normal cells and in other respects atypical. The nucleus, though often notched or indented, gives the staining reaction of the small lymphocyte nucleus and occupies almost the entire cell. The small lymphocytes present in this group of cases were on the whole less atypical than those met with in the acute cases, but it is impossible to distinguish the acute from the chronic disease by an examination of the cells only.

In Case 1 and Case 6 the lymphocytes were of the large type, forming

a variety of leukaemia which we believe to be the rarest of all forms of 'primary' blood disease. We have never seen an acute disease associated with a predominance of cells of this type. In Case 6 the cells were perfectly typical large lymphocytes and contained azur granules. In Case 1 the cells were undoubtedly of this type, but the granules were absent.

The cells of Cases 1, 3, and 6 were examined by the oxydase reaction and no granules were seen in them.

The predominance of the lymphocytes was very marked in all the cases and they commonly formed from 80 to 90 per cent. of all the leucocytes.

The total number of leucocytes was considerable, and on the whole approached that met with in myeloid leukaemia. The leucocytosis was generally much in excess of that met with in acute lymphoid leukaemia.

Fluctuations in the number or in the varieties of the white cells were inconspicuous, and remarkably little change occurred either from the progress of the disease or in response to treatment. The condition in this respect differs strikingly from that of myeloid leukaemia.

The red cells and haemoglobin were scarcely affected in the majority of cases, but a marked secondary anaemia developed as the disease progressed.

*Diagnosis.* The first step in diagnosis is the discovery of splenic or glandular enlargement, since in all such cases an examination of the blood is essential. On clinical grounds the condition most closely resembles chronic myeloid leukaemia. There is in the early stages an absence of grave symptoms, together with considerable splenic and, very much less commonly, marked glandular enlargement. The differential points in the clinical diagnosis between chronic myeloid and chronic lymphoid leukaemia are of little value.

The average age of incidence is distinctly later in lymphoid leukaemia, and the disease is more chronic and is less influenced by treatment.

The diagnosis is certainly made by a blood examination, coupled with a knowledge of the clinical condition of the patient. A chronic illness accompanied by little general disturbance and a blood picture, such as any of those described in Table VI, is chronic lymphoid leukaemia. A knowledge of the clinical condition is essential, since we cannot certainly recognize the variety of lymphæmia from the nature of the cell present, although it is possibly true that the rare cases associated with lymphocytes of the large variety always run a chronic course.

*Duration of the disease.* Of the two fatal cases one was under observation for seven months, and it is quite uncertain how long the splenic enlargement had been present. The other case gave a history of nine weeks' illness, but had not then observed the enlargement of his spleen. He left hospital apparently in comparatively good health, but died three months later.

Of the 4 non-fatal cases one, discovered by chance, has been under observation for five months and is now in good health. One gave a two years' history of splenic enlargement, and now, a year later, is in fair health. One gave a previous history of two years' glandular enlargement, and has since been

under observation for two years. Another case has been under observation for five years.

*Prognosis.* The prognosis appears to be less grave in this variety than in any other form of leukaemia, and it is possible that the large cell type is more favourable than the small cell. It is certain that subjects of this disease may live for five years or more in comparative health, but we have seen no indication of cure in any case.

Five of the cases received arsenic and 2 were given X-rays. In one case there was a marked decrease in the size of the glands as the result of X-ray treatment, but the glands have subsequently returned to the previous size. The blood has been little, if at all, affected. This case has been given also intravenous injections of salvarsan, but with no result.

Another case was given nucleinic acid, sodium cinnamate, and *Staphylococcus aureus* vaccine, with the object of obtaining an increase in the polynuclear cells. There was no response whatever to the injections.

The general effect of arsenical and X-ray treatment upon the blood and the spleen is much less marked than that obtained in the majority of cases of chronic myeloid leukaemia.

#### *Remarks.*

Of 59 consecutive cases of leukaemia, 16 have been classed as acute myeloid, 29 as chronic myeloid, 8 as acute lymphoid leukaemia, and 6 as chronic lymphoid.

It is evident that the clinical picture of leukaemia varies with the acuteness or chronicity of the disease, and not with the lymphoid or myeloid origin of the cells. Acute lymphoid and acute myeloid leukaemia are clinically indistinguishable, and so may be chronic lymphoid and chronic myeloid leukaemia. Acute lymphoid leukaemia has little resemblance to chronic lymphoid, nor acute myeloid to chronic myeloid, except in so far as chronic myeloid may terminate by a condition similar to the acute disease.

We can distinguish by a blood examination between the acute and chronic types of myeloid leukaemia, but not between acute and chronic lymphoid leukaemia. The latter diseases are readily distinguished upon clinical grounds. Acute myeloid and acute lymphoid leukaemia can be distinguished by the type of cell present, but the conditions have been frequently confused and the clinical course is the same. The confusion has been due to a failure in distinguishing between myeloblasts and lymphocytes. The differentiation is rarely if ever difficult for those accustomed to the use of Leishman's or other similar stains. In this connexion we have found the oxydase reaction to be quite useless.

In no case in our experience has the myeloid type of cell been replaced by the lymphoid type, or vice versa.

The effect of treatment in the acute cases has been negligible. In the chronic

lymphoid cases, changes have been extremely slight. In the chronic myeloid cases, some have changed little, others have changed to a remarkable degree. Those cases which have fluctuated to the greatest extent have been the youngest subjects. The blood of patients over the middle age reacts but little.

There has been no instance of purpura in either of the chronic leukaemias. In those cases of acute leukaemia associated with purpura the spleen was invariably enlarged. Infiltrations of the skin, painful bones, and priapism occurred in no case. Oral sepsis did not appear to have any bearing upon any type of the disease.

The cases of acute myeloid leukaemia include an interesting group of 4 patients whose predominant blood-cell was a so-called Rieder cell. This cell we believe to be a large hyaline, partly on morphological grounds since the cell may be indistinguishable from the large hyaline of normal blood, and intermediate types between the normal cell and the primitive marrow-cell were numerous; partly on functional grounds, because these cells were actively phagocytic as are those of the normal blood. We consider that a scrutiny of these cases affords strong evidence of the marrow origin of the large hyaline cell.

The brief extracts of the post-mortem examinations are taken from Dr. H. M. Turnbull's reports. We are indebted to the staff of the London Hospital for permission to make use of the cases under their care.

The original drawings from which Plate 26 has been prepared have been reproduced previously in the *Folia Haematologica*. For permission to make use of them, we are indebted to the Editor, Professor A. Pappenheim.

TABLE I. *Acute Myeloid Leukaemia.*

Number of Case.	Age (years).	Duration under observation.	Lymphatic Glands.	Spleen.	Purpura.	Haemorrhages.	Date.	Erythrocytes per c.mm.	Haemoglobin %.	Colour Index.	Leucocytes per c.mm.	Differential Count																	
												Polynuclear Neutrophils %.	Eosinophils %.	Small Lymphocytes %.	Large Lymphocytes %.	Hyalines %.	Mast Cells %.	Transitional Neutrophils %.	Myelocytes %.	Neutrophils %.	Myelocytes %.	Basophil %.	Myelocytes %.	Amphophil %.	Myeloblasts %.	Normoblasts per 100 leucocytes.	Megakaryoblasts per 100 leucocytes.		
(1) R. G.	5	3 months	0	0	0	+	3/7/13	3,700,000	60	0.8	1,400	19.0	0.5	15.0	14.0	2.0	—	—	1.0	1.0	—	—	—	—	—	48.5	0.5	—	—
							10/7/13	—	—	—	1,800	16.0	0.5	27.5	12.0	1.0	—	—	0.5	—	—	—	—	—	—	41.0	—	—	—
							28/8/13	1,930,000	20	0.5	13,800	1.5	—	0.5	—	—	—	—	—	—	—	—	—	—	—	98.0	—	—	—
							5/9/13	1,000,000	10	0.5	2,700	2.5	1.0	1.0	1.5	—	—	—	—	—	—	—	—	—	—	94.0	—	—	—
(2) F. K.	64	?	0	0	0	0	18/10/09	1,025,000	15	0.75	17,000	8.8	—	—	—	—	—	—	0.8	—	—	—	—	—	—	89.0	1.2	0.2	—
(3) E. P.	3	4 weeks	+	0	0	0	27/1/13	2,100,000	25	0.6	1,800	23.5	2.5	52.5	12.0	6.5	0.5	0.2	2.5	—	—	—	—	—	—	49.5	2.0	—	—
							5/2/13	—	30	—	7,200	25.0	1.0	13.0	1.5	2.0	0.5	8.5	—	—	—	—	—	—	—	79.0	—	—	—
(4) A. T.	7	6 weeks	+	+	+	+	13/2/13	—	—	—	18,200	8.5	3.0	1.0	—	—	—	3.5	—	—	—	—	—	—	—	99.5	0.2	—	—
							9/2/10	3,400,000	60	0.9	150,000	0.4	—	—	—	0.1	—	—	—	—	—	—	—	—	—	99.5	0.2	—	—
							16/2/10	—	—	—	140,000	1.4	—	—	—	0.4	—	—	0.2	—	—	—	—	—	—	98.8	0.2	—	—
(5) B. D.	15	2 weeks	+	+	+	0	1/3/10	—	—	—	140,000	0.6	0.2	—	—	—	—	—	—	—	—	—	—	—	—	98.8	0.2	—	—
							15/9/13	3,500,000	65	0.9	170,000	3.5	—	1.0	2.0	—	—	—	0.2	—	—	—	—	—	—	98.8	0.2	—	—
							20/9/13	—	—	—	100,000	2.0	—	2.0	1.5	—	—	—	—	—	—	—	—	—	—	93.5	—	—	—
							27/9/13	1,650,000	25	0.8	90,000	—	—	—	—	—	—	—	—	—	—	—	—	—	—	94.5	—	—	—
(6) A. L.	28	2 weeks	+	+	+	+	26/4/10	2,500,000	40	0.8	88,200	3.3	—	7.2	—	0.3	—	—	0.3	—	—	—	—	—	—	88.9	0.5	1.0	—
							2/5/10	1,380,000	20	0.7	50,000	6.8	—	0.8	—	1.0	—	—	—	—	—	—	—	—	—	92.4	1.0	0.8	—
(7) L. C.	6	2 days	+	+	0	0	22/2/11	1,700,000	15	0.4	7,200	8.0	0.5	—	—	2.4	—	—	0.8	—	—	—	—	—	—	91.2	—	—	—
							23/2/11	—	—	—	—	4.4	0.4	3.0	—	7.0	—	—	—	—	—	—	—	—	—	79.5	—	—	—
(8) J. P.	40	3 days	+	+	0	0	17/1/11	—	—	—	68,000	10.5	—	—	—	—	—	—	—	—	—	—	—	—	—	73.5	—	0.5	—
(9) M. L.	14	2 weeks	+	+	+	+	29/8/13	1,312,000	15	0.6	8,000	10.5	—	9.5	3.0	—	—	—	3.5	1.0	—	—	—	—	—	60.0	—	—	—
							2/9/13	862,000	10	0.6	6,900	28.5	—	3.0	4.0	—	—	—	0.2	—	—	—	—	—	—	99.4	—	—	—
(10) M. S.	15	3 weeks	+	+	0	0	4/9/13	1,600,000	35	1.1	200,000	0.4	—	—	—	—	—	—	0.2	—	—	—	—	—	—	99.6	—	0.2	—
							7/9/13	—	—	—	—	0.2	—	—	—	—	—	—	0.6	—	—	—	—	—	—	98.6	—	0.6	—
(11) L. C.	40	4 days	0	+	0	+	14/9/13	1,500,000	25	0.8	420,000	0.8	—	—	—	—	—	—	0.6	—	—	—	—	—	—	3.2	0.2	0.8	—
(12) L. H.	12	2 weeks	+	+	0	+	28/4/09	840,000	10	0.6	228,000	1.6	0.6	15.6	2.0	73.0	—	—	0.8	—	—	—	—	—	—	98.6	—	0.6	—
							1/12/11	2,240,000	40	0.9	160,000	4.0	0.6	8.4	0.6	79.0	—	—	0.4	3.4	0.4	—	—	—	—	3.2	0.2	0.2	—
							7/12/11	2,800,000	60	0.9	260,000	2.8	0.2	5.0	1.2	88.4	—	—	0.4	1.8	0.2	—	—	—	—	—	—	—	—
							12/12/11	2,600,000	35	0.6	228,000	1.6	—	5.6	1.0	89.0	—	—	3.8	—	—	—	—	—	—	—	—	—	—
(13) E. D.	10	6 weeks	+	+	0	+	8/10/12	1,950,000	35	0.9	20,000	4.0	0.5	14.0	4.0	30.5	1.0	—	4.0	—	—	—	—	—	—	45.0	0.5	1.0	—
							18/10/12	1,850,000	25	0.7	32,000	1.5	0.5	14.0	1.5	40.5	—	—	4.0	0.5	—	—	—	—	—	35.0	—	—	—
							28/10/12	1,650,000	25	0.7	60,000	1.5	—	10.0	1.0	62.5	1.0	—	1.5	—	—	—	—	—	—	22.5	0.2	—	—
							7/11/12	960,000	15	0.7	30,000	5.0	—	23.0	0.5	46.0	1.0	—	1.5	—	—	—	—	—	—	21.0	1.0	1.5	—
							15/11/12	715,000	10	0.7	32,000	2.0	—	13.5	2.0	45.5	1.0	—	1.5	—	—	—	—	—	—	33.0	0.5	0.5	—
(14) E. V.	43	3 days	0	+	0	+	27/1/13	1,300,000	15	0.5	43,000	7.2	—	9.8	0.2	61.6	—	—	2.2	5.6	—	—	—	—	—	13.0	—	0.8	—
(15) P. T.	37	2 weeks	0	0	0	0	14/8/11	1,350,000	20	0.7	1,600	35.5	—	27.0	15.0	0.5	17.0	—	1.0	1.5	—	—	—	—	—	—	—	—	—
							24/8/11	—	—	—	2,000	24.6	2.6	28.8	13.0	0.4	12.6	—	3.2	3.4	2.0	9.2	—	—	—	—	7.0	8.0	—
(16) E. P.	23	3 weeks	+	+	+	+	17/8/11	1,000,000	15	0.7	30,000	41.0	0.6	10.8	11.8	7.4	0.8	—	0.2	—	—	—	—	—	—	—	8.0	7.0	—
							21/8/11	800,000	10	0.6	34,000	47.5	—	19.0	12.0	4.5	—	—	1.0	1.60	—	—	—	—	—	—	25.0	42.0	—
							30/8/11	580,000	8	0.7	70,000	27.0	—	5.5	4.0	3.5	—	—	0.5	59.5	—	—	—	—	—	—	45.0	35.0	—
							1/9/11	550,000	8	0.7	70,000	31.5	—	4.5	0.5	2.5	—	—	61.0	—	—	—	—	—	—	—	—	—	—

TABLE II. *Chronic Myeloid Leukaemia.*

## Group I. Great Variations.

Number of Case.	Age (years).	Duration.	Alive or dead.	Date.	Erythro- cytes per c.mm.	Haemoglobin %.	Colour Index.	Leuco- cytes per c.mm.	Polynuclear Neutrophils %.	Polynuclear Eosinophils %.	Small Lymphocytes %.	Large Lymphocytes %.	Large Hyalines %.	Mast Cells %.	Transitional Neutrophils %.	Myelocytes Neutrophil %.	Myelocytes Eosinophil %.	Basophil %.	Myelocytes Amphophil %.	Myeloblasts %.	Normoblasts per 100 leucocytes.	Megaloblasts per 100 leucocytes.
(1)	J. B. 17	2 years	dead	12/7/09	—	—	—	218,000	68.6	2.8	3.2	3.0	1.4	1.4	—	19.2	0.4	—	—	—	—	0.6
				28/8/09	—	—	—	27,500	60.6	3.6	10.6	3.8	5.0	6.2	—	10.0	0.2	—	—	—	—	0.6
				6/8/11	—	—	—	100,000	31.8	1.8	1.8	6.4	1.0	3.6	11.6	38.6	1.4	—	0.6	1.4	—	—
				31/3/11	—	—	—	26,000	52.5	4.5	2.5	4.5	2.5	18.0	2.5	13.0	—	—	—	—	—	1.5
				21/4/11	—	—	—	5,400	13.5	5.0	4.5	2.0	1.5	25.5	1.0	5.5	0.5	—	—	40.0	11.5	10.0
(2)	C. F. 17	2 years	dead	25/8/09	2,325,000	35	0.7	55,200	54.0	4.0	12.8	8.4	3.6	4.4	—	11.6	1.2	—	—	—	12.0	12.0
				2/10/09	—	—	—	4,200	41.0	3.0	41.0	11.0	2.0	2.0	—	—	0.4	—	—	—	5.0	4.0
				6/4/10	2,400,000	35	0.7	21,200	30.0	0.8	17.4	33.0	1.2	7.4	1.2	8.0	0.4	—	0.6	—	3.0	2.0
				4/5/10	—	—	—	47,000	49.5	—	12.5	5.5	1.0	2.5	—	7.0	—	—	—	22.0	32.5	10.5
				20/6/10	—	—	—	96,000	24.0	1.0	3.5	0.5	—	4.5	—	18.5	3.0	—	—	45.0	4.5	3.0
(3)	A. K. 33	1½ years	dead	9/5/10	3,875,000	50	0.6	230,000	65.0	1.6	1.8	2.4	1.4	6.0	4.6	16.6	0.6	—	—	—	0.6	0.5
				2/7/10	4,200,000	55	0.6	4,000	78.0	1.0	5.5	2.5	2.0	9.5	—	1.5	—	—	—	—	4.0	0.5
				31/8/10	—	—	—	1,020	17.0	—	60.0	19.0	4.0	—	—	—	1.5	—	—	—	1.0	1.0
				27/3/11	—	75	—	30,000	47.0	—	2.5	3.5	1.0	21.8	2.5	12.2	1.5	—	—	8.0	0.5	—
				26/4/11	—	—	—	5,000	76.0	2.5	1.5	7.5	2.5	8.0	4.5	11.0	—	—	—	—	—	—
				30/5/11	6,100,000	85	0.7	54,000	59.5	0.5	3.0	9.0	2.0	10.5	—	2.5	1.0	—	—	—	—	—
				1/7/11	—	—	—	15,000	48.0	2.0	11.5	24.0	2.0	9.0	1.0	4.0	—	—	—	—	—	—
				10/7/11	—	—	—	7,400	28.0	4.0	10.5	23.0	6.5	23.0	1.0	2.8	—	—	—	—	0.2	0.6
(4)	P. N. 11	1 year	dead	15/11/10	4,100,000	70	0.9	180,000	54.6	1.2	3.2	5.2	8.0	2.8	—	17.0	1.4	—	—	—	—	—
				14/12/10	—	65	—	16,000	64.0	1.0	6.0	5.5	5.5	6.5	—	11.5	—	—	—	—	—	—
				16/3/11	—	—	—	5,000	67.0	1.5	16.5	10.0	4.0	1.0	—	—	—	—	—	—	—	—
				4/9/11	—	—	—	10,000	68.5	1.0	18.0	7.0	2.5	0.5	0.5	2.0	—	—	—	—	—	—
				21/9/11	4,726,000	80	0.8	4,600	67.0	0.5	19.5	8.0	2.5	1.5	—	1.0	—	—	—	42.5	0.2	0.6
				5/10/11	—	—	—	3,400	25.5	—	20.0	8.5	1.0	0.5	—	1.0	0.5	—	—	98.0	—	—
				17/10/11	1,550,000	10	0.3	30,000	2.0	—	—	—	—	—	—	—	—	—	—	—	—	—
(5)	E. I. 30	2 years	dead	20/3/11	4,500,000	65	0.7	100,000	40.0	0.5	1.5	5.0	1.0	11.5	5.0	34.0	1.0	—	—	0.5	1.0	—
				26/4/11	—	—	—	6,200	53.5	0.5	6.0	9.0	6.0	15.0	—	10.0	—	—	—	—	—	—
				9/8/11	—	—	—	8,600	47.5	0.5	23.0	8.5	1.5	19.0	—	—	—	—	—	—	—	—
				29/12/11	—	70	—	150,000	44.3	2.0	3.0	1.5	2.2	7.0	7.0	25.5	—	—	—	—	—	—
				15/1/12	4,500,000	75	0.8	50,000	66.6	0.6	1.8	1.4	0.6	16.2	0.6	15.2	0.2	—	—	5.7	0.5	0.5
				4/3/12	1,800,000	25	0.7	69,000	3.4	—	—	—	—	—	—	—	—	—	—	94.6	0.8	0.2
				8/3/12	725,000	10	0.7	3,800	7.5	—	—	—	—	—	0.6	1.0	—	—	—	22.0	0.2	—
				12/3/12	—	—	—	1,400	29.0	—	—	—	—	—	—	2.5	—	—	—	61.5	—	—
(6)	H. C. 8	1½ years	dead	25/3/11	3,650,000	65	0.9	30,000	19.0	0.5	10.0	7.0	0.5	11.5	4.0	33.0	2.0	—	1.0	5.0	1.0	1.0
				7/4/11	—	—	—	15,000	49.0	0.5	3.5	5.0	0.5	4.5	3.0	30.0	2.0	—	—	—	1.0	—
(7)	F. G. 20	2½ years	dead	27/11/11	4,500,000	75	0.8	35,000	64.2	1.0	3.6	2.2	2.8	4.2	4.2	16.2	0.2	—	—	1.4	1.5	—
				21/10/12	5,900,000	85	0.7	18,400	67.8	0.4	4.2	1.4	3.0	3.0	6.4	12.0	0.2	—	—	0.6	0.6	—
				15/11/12	4,700,000	60	0.6	5,600	74.0	—	8.5	3.5	1.0	4.5	—	4.0	—	—	—	2.0	—	—



TABLE III. *Chronic Myeloid Leukaemia.*

## Group II. Moderate Variations.

Number of Case.	Age (years).	Duration.	Alive or dead.	Date.	Erythro- cytes per c.mm.	Haemoglobin %.	Colour Index.	Leuco- cytes per c.mm.	Polynuclear Neutrophils %.	Polynuclear Eosinophils %.	Small Lymphocytes %.	Large Lymphocytes %.	Hyalines %.	Mast Cells %.	Transitional Neutrophils %.	Polynuclear Neutrophils %.	Myelocytes Neutrophil %.	Myelocytes Eosinophil %.	Myelocytes Basophil %.	Myelocytes Amphophil %.	Myeloblasts %.	Normoblasts per 100 leucocytes.	Megaloblasts per 100 leucocytes.
(8)	E. H. 43	1½ years	dead	15/6/09	3,010,000	35	0.6	180,000	40.2	1.4	4.0	8.6	1.6	6.0	10.2	25.2	2.4	—	—	—	—	2.0	1.0
				22/7/10	3,850,000	45	0.6	28,000	34.5	0.5	15.5	22.0	1.0	9.0	—	16.0	0.5	—	—	—	—	3.5	0.5
(9)	D. T. 33	1½ years	dead	16/9/10	4,400,000	65	0.7	240,000	35.4	3.2	3.2	8.4	1.6	4.6	—	21.2	2.4	—	—	—	—	1.5	1.0
				3/10/10	—	—	—	120,000	54.2	1.8	3.4	10.6	3.6	0.6	—	22.6	3.2	—	—	—	—	2.0	1.0
				23/12/10	—	—	—	60,000	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
				5/1/11	—	—	—	70,000	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
(10)	D. H. 19	3 years	dead	3/2/11	2,500,000	35	0.7	300,000	51.0	4.0	2.2	5.6	1.2	6.6	5.2	22.6	1.6	—	—	—	—	0.6	—
				1/4/11	—	—	—	79,000	53.2	0.6	2.0	2.0	0.6	7.0	7.2	27.2	0.2	—	—	—	—	—	—
				27/4/11	—	—	—	10,840	87.5	4.5	1.5	2.0	—	4.0	—	0.5	—	—	—	—	—	—	—
				2/6/11	6,100,000	85	0.7	5,400	84.0	—	8.0	1.5	1.5	4.5	0.5	—	—	—	—	—	—	—	—
				3/11/11	—	—	—	39,000	61.5	0.5	1.5	2.0	—	5.5	6.5	20.5	1.0	—	—	—	—	—	0.5
				29/11/11	—	—	—	68,000	65.4	1.2	1.2	1.6	1.4	3.4	4.2	20.6	—	—	—	—	—	—	—
				14/12/11	4,950,000	85	0.9	37,000	73.8	0.6	2.6	1.2	0.2	5.0	4.0	11.6	—	—	—	—	—	—	—
				29/12/11	—	—	—	9,000	63.2	2.0	9.4	3.8	1.8	9.8	0.8	7.4	—	1.8	—	—	—	—	0.5
(11)	F. S. 35	3½ years	alive	15/2/11	—	—	—	120,000	69.5	1.5	3.0	4.5	1.5	2.5	—	17.5	—	—	—	—	—	—	—
				15/5/12	4,800,000	85	0.8	43,400	58.0	1.5	5.5	1.5	5.0	8.0	4.0	15.0	—	—	—	—	—	—	—
				24/10/13	3,700,000	70	0.9	100,000	69.5	1.0	4.0	3.5	1.0	4.0	5.5	6.5	0.5	—	—	—	—	—	—
(12)	E. E. 57	3½ years	alive	1/9/11	2,650,000	45	0.8	600,000	51.0	2.0	1.5	2.0	1.0	2.5	6.0	27.0	1.0	—	—	—	—	0.5	—
				28/9/11	1,820,000	30	0.8	112,000	61.2	0.2	3.8	0.4	0.2	0.6	5.8	25.2	—	—	—	—	—	2.0	3.5
				7/10/11	—	—	—	42,000	60.0	0.5	6.0	6.5	0.5	13.0	2.5	9.0	—	—	—	—	—	2.0	0.2
				20/11/11	3,750,000	60	0.8	168,000	56.4	0.4	1.8	0.8	0.4	3.0	3.8	27.2	0.2	0.2	—	—	—	0.5	—
(13)	G. D. 51	2½ years +	?	13/6/12	2,600,000	40	0.7	152,000	55.5	1.0	1.0	0.5	2.5	2.5	5.5	21.0	—	—	—	—	—	1.0	—
				4/7/12	3,050,000	40	0.7	52,000	56.2	3.0	3.4	1.8	1.2	7.0	4.0	15.8	0.4	—	—	—	—	0.2	—
(14)	J. T. 35	2½ years	alive	27/6/12	3,650,000	70	0.9	74,000	61.0	0.6	1.6	0.8	0.6	1.2	5.0	27.2	0.2	—	—	—	—	1.0	—
				1/1/13	4,100,000	75	0.9	64,000	69.0	—	2.5	1.5	1.5	4.5	3.5	16.0	—	—	—	—	—	—	—
				19/5/13	5,300,000	80	0.8	18,000	62.0	0.4	3.6	0.4	1.0	3.0	4.2	24.0	0.4	—	—	—	—	0.4	—
				8/10/13	3,600,000	50	0.7	102,000	60.2	1.0	1.4	0.4	—	5.0	3.4	22.4	1.6	—	—	—	—	0.4	0.2

TABLE IV. *Chronic Myeloid Leukaemia.*  
Group III. Slight Variations.

Number of Case.	Age (years).	Duration.	Date.	Erythro- cytes per c.mm.	Haemoglobin %.	Colour Index.	Leuco- cytes per c.mm.	Polynuclear Neutrophils %.	Polynuclear Eosinophils %.	Small Lymphocytes %.	Large Lymphocytes %.	Hyalines %.	Mast Cells %.	Transitional Neutrophils %.	Myelocytes Neutrophils %.	Myelocytes Eosinophils %.	Basophil %.	Myelocytes Amporphil %.	Myeloblasts %.	Normoblasts per 100 leucocytes.	Megakaryoblasts per 100 leucocytes.	
(15) F. C.	30	?	4/2/09 4/3/09 2/4/09	3,060,000 — 2,300,000	60 — 35	1.0 — 0.7	186,000 240,600 230,800	67.2 63.0 61.4	4.0 8.4 3.2	2.8 2.0 2.4	5.2 3.5 3.8	3.2 2.0 3.2	5.8 6.8 5.4	2.6 2.6 6.0	10.4 10.6 14.0	1.0 0.8 0.4	— — —	— — —	— — —	1.0 2.0 0.5	0.5 1.0 —	
(16) L. C.	56	5 months	—	—	—	—	181,600	60.8	0.2	1.6	1.8	3.6	5.6	5.8	19.8	0.6	—	—	—	—	—	
(17) C. O.	40	1 year	17/2/09 6/9/09 30/12/09	2,300,000 2,540,000 —	30 40 40	0.6 0.8 0.8	88,400 100,000 120,000	58.6 49.4 36.0	3.4 5.4 3.2	4.2 5.2 8.6	3.4 3.6 8.6	3.6 8.2 16.0	5.6 15.6 4.8	7.4	12.2	2.0	—	—	—	1.0	0.5	
(18) D. S.	38	2½ years	23/4/10 23/12/09 20/7/10	1,975,000 3,175,000 —	30 60 60	0.7 0.9 0.9	360,000 96,000 215,000	36.0 61.6 56.5	3.6 3.6 1.5	1.4 4.4 1.5	2.2 2.6 3.5	1.0 3.5 5.5	6.0 6.0 5.0	7.0	11.5	—	—	—	—	5.5	8.0	
(19) R. S.	52	5 years	19/5/11 20/6/11	2,500,000 —	50 —	1.0 —	40,000 11,000	57.0 37.0	5.0 9.0	1.5 17.0	0.5 7.5	5.5 3.0	5.0 5.0	7.0	14.5	—	—	—	—	—	5.0	5.0
(20) I. S.	44	1½ years	14/8/11 28/8/11 29/9/11	— 2,900,000 —	— 50 —	— 0.8 —	32,000 380,000 240,000	70.5 37.0 42.6	2.8 5.8 5.8	0.8 0.4 0.4	4.6 1.6 1.6	0.6 1.0 7.0	10.4 2.4 2.4	3.0	9.0	0.5	0.5	—	—	7.0	4.0	
(21) B. L.	49	2½ years	29/5/12 17/10/11 17/5/12	2,500,000 4,000,000 3,900,000	40 80 65	0.8 1.0 0.8	190,000 120,000 68,800	47.0 51.2 53.3	4.5 4.3 4.0	0.5 1.0 2.3	0.5 3.0 0.7	0.3 0.3 0.7	1.0 1.0 0.7	5.5	21.0	2.5	0.3	—	5.4	1.0	—	
(22) F. M.	40	?	5/3/13 15/7/13 19/12/11	— 3,050,000 —	— 50 —	— 0.8 —	52,000 244,000 120,000	58.4 45.5 59.5	1.4 3.0 3.5	2.6 0.5 1.5	2.0 2.5 1.0	0.2 0.5 3.5	6.2 8.5 3.5	5.2	15.2	1.0	—	—	10.2	4.0		
(23) S. K.	44	2½ years	28/12/11 19/12/11 3/1/12	2,500,000 3,550,000 3,550,000	40 50 55	0.8 0.7 0.8	240,000 133,000 70,000	52.0 56.8 30.8	2.0 1.2 4.8	1.0 0.8 3.4	1.0 0.2 0.2	— — —	15.0	6.0	20.5	0.8	0.4	—	0.5	2.0	1.0	
(24) H. S.	18	2½ years	2/2/12 16/2/12 14/5/12	3,450,000 4,140,000 4,400,000	60 65 70	0.7 0.7 0.7	134,000 82,000 130,000	52.0 64.5 61.0	3.5 2.0 0.5	1.5 3.0 1.0	1.5 2.0 2.5	0.5 0.5 1.5	6.0 3.5 2.0	5.0	22.5	2.5	—	—	3.0	2.0	1.0	
(25) S. W.	50	2½ years	10/7/12 25/6/12 11/7/12	4,600,000 4,300,000 5,200,000	70 60 60	0.8 0.6 0.6	186,000 170,000 160,000	59.5 50.0 54.5	0.5 0.4 2.0	0.5 1.6 2.5	0.5 0.6 1.0	1.5 1.5 0.5	11.8	—	19.8	3.4	1.0	—	9.4	2.0		
(26) I. M.	47	8 months	12/2/13 1/3/13 27/3/13	3,400,000 2,760,000 3,200,000	40 45 55	0.8 0.9 —	174,000 170,000 230,000	54.5 54.5 51.5	1.0 2.0 1.5	2.0 1.5 1.5	2.0 2.5 1.5	0.5 0.5 2.0	3.0 2.0 2.5	2.5	23.5	2.0	—	—	11.5	4.0		
(27) L. D.	66	2 years	16/7/13 19/6/13 7/8/13	2,700,000 — —	45 — —	0.8 — —	220,000 220,000 220,000	57.5 51.0 51.0	0.5 1.5 1.5	1.0 0.5 0.5	1.0 0.5 0.5	1.0 1.0 1.2	2.5 6.5 9.6	6.5	29.5	1.0	—	—	1.5	3.0		
(28) G. G.	37	?	28/6/09	1,975,000	30	0.7	292,000	42.0	7.2	5.4	7.0	1.2	3.6	7.0	23.5	0.5	—	—	8.0	1.0		
(29) E. C.	66	?	16/10/12	3,100,000	35	0.5	350,000	61.2	2.0	0.4	0.4	—	5.4	2.8	24.0	1.2	—	—	2.4	1.0		



TABLE VI. *Chronic Lymphoid Leukaemia.*

Number of Case.	Age (years).	Duration.	Alive or dead.	Date.	Erythro- cytes per c. mm.	Haemoglobin %.	Colour Index.	Leuco- cytes per c. mm.	Polynuclear Neutrophils %.	Eosinophils %.	Small Lymphocytes %.	Large Lymphocytes %.	Hyalines %.	Mast Cells %.	Myelocytes Neutrophil %.	Myeloblasts %.	Normoblasts per 100 leucocytes.	Megaloblasts per 100 leucocytes.
(1)	I. C. 45	5½ years	alive	15/10/08	4,580,000	85	0.9	21,000	—	—	—	67.0	—	—	—	—	0.2	—
				18/12/11	3,500,000	65	0.9	150,000	5.0	—	0.6	93.0	1.2	—	—	—	0.2	—
				26/3/13	1,600,000	40	1.3	106,000	1.4	0.2	0.4	97.4	0.2	—	—	0.4	1.0	0.6
(2)	A. S. 62	5 months	dead	10/12/13	1,240,000	10	0.4	100,000	1.0	—	—	98.6	0.2	0.2	—	—	—	—
				11/5/11	4,550,000	80	0.9	18,800	5.2	—	92.0	1.2	1.6	—	—	—	—	—
(3)	D. F. 40	4 years	alive	13/6/11	—	—	—	62,200	4.0	—	93.0	2.0	1.0	—	—	—	—	—
				6/2/12	4,600,000	95	1.0	37,000	4.4	0.2	93.8	0.4	1.2	—	—	1.2	—	—
				15/7/12	3,900,000	90	1.1	40,000	3.2	1.2	93.2	0.2	0.8	0.2	—	—	—	—
(4)	I. B. 50	7 months	dead	15/11/13	4,200,000	85	1.0	43,000	1.0	—	93.5	5.0	—	0.5	—	—	—	—
(5)	E. P. 67	3 years	alive	13/6/12	1,800,000	35	1.0	154,000	—	—	89.6	1.4	—	—	—	1.0	—	—
				7/11/12	5,600,000	100	0.9	17,000	1.5	—	89.5	8.0	—	—	—	—	—	—
				12/9/13	3,850,000	65	0.8	11,800	16.5	2.0	39.5	40.0	2.0	—	—	—	—	—
(6)	B. F. 50	5 months	alive	20/10/13	4,850,000	80	0.8	7,000	10.0	0.2	1.6	87.2	1.0	—	—	—	—	—
				9/12/13	—	—	—	11,400	6.0	—	27.0	67.0	—	—	—	—	—	—

## DESCRIPTION OF PLATE.

PLATE 26, FIG. 1. *Myeloblasts*. From Case 5, Table II. This is the cell usually occurring in acute myeloblastic leukaemia and in the acute myeloblastic termination of chronic myeloid leukaemia. Small numbers are constantly present in chronic myeloid leukaemia.

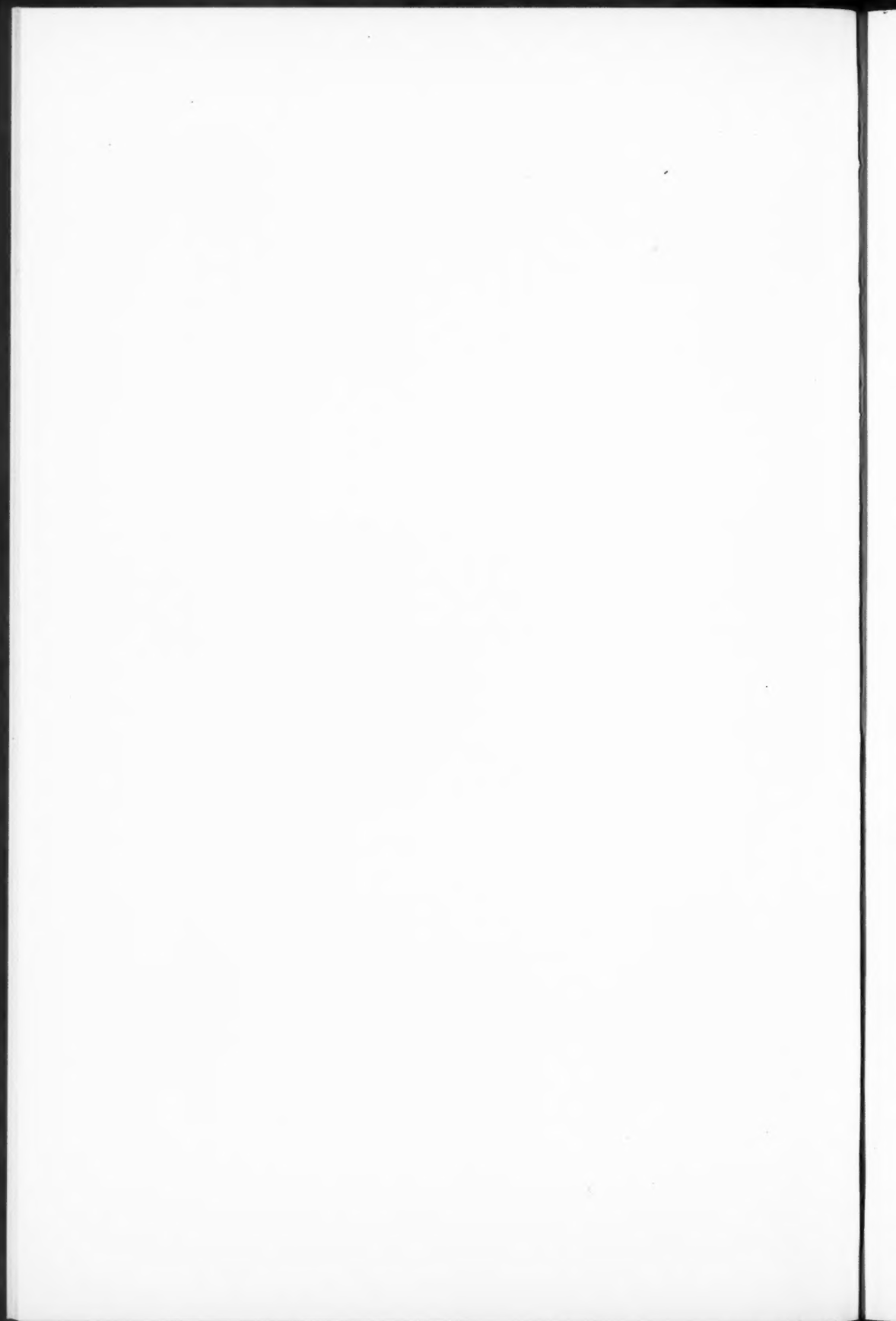
FIG. 2. *Micromyeloblasts*. From Case 4, Table II. This variety of myeloblast is much rarer than the cell illustrated in Fig. 1.

FIG. 3. *Hyaline myeloblasts*. From Case 11, Table I. This type of cell, with slight variations, was present in this and Cases 12, 13, and 14, Table I.

FIG. 4. *Large lymphocytes*, from a case of chronic lymphoid leukaemia. Case 1, Table VI

FIG. 5. *Normal cells of blood* (for comparison). The figure illustrates a large lymphocyte with azur granules, a small lymphocyte, a large hyaline and a red cell.

The cells in all the figures are drawn to the scale of the red cell.





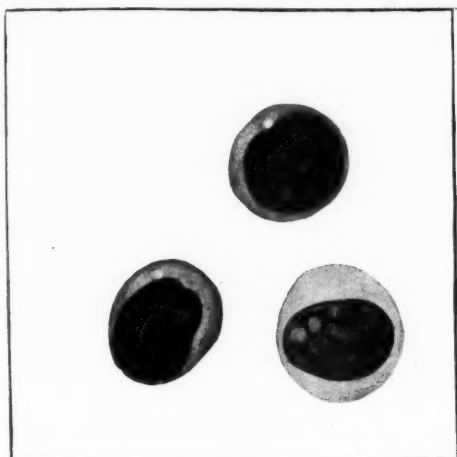


FIG. 1

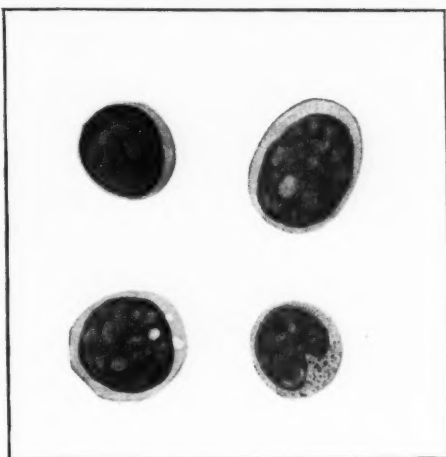


FIG. 2

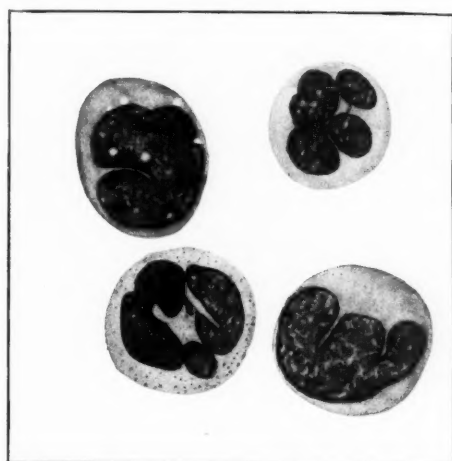


FIG. 3



FIG. 4

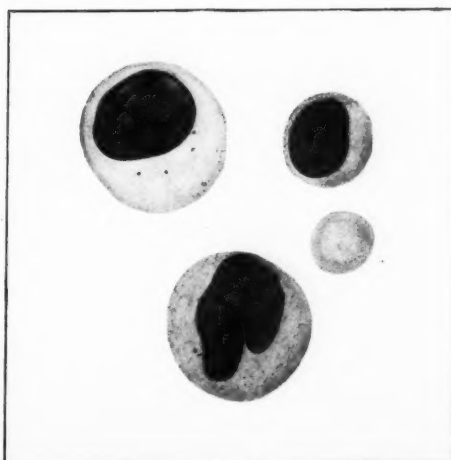


FIG. 5



# THE FRAGILITY OF THE RED BLOOD CORPUSCLES IN PHYSIOLOGICAL AND PATHOLOGICAL STATES

By ALFRED DOUGLAS BIGLAND

(From the Biochemical Laboratory, University of Liverpool)

With Plate 27

## *Introductory.*

MUCH work has been done upon the red corpuscle of recent years, but for the most part only reactions depending upon it have attracted the minds of clinicians. The study of the red corpuscle, as such, in health and disease has not been pursued with the same zeal. A large number of attempts, however, have been made to determine corpuscular fragility in various diseases, but as the results have been so varying it seems only too evident that there is room for more work on this subject. To fill a small portion of this gap in our knowledge, or rather to point a possible way to the filling thereof, is the object of this work.

Haemolysis may be defined as the breaking up of the red corpuscle in such a manner that the haemoglobin contained within it is liberated. The agents by which this process is accomplished fall into four groups:

1. *The Mechanical*, such as grinding up corpuscles with sand.
2. *The Physico-chemical*, such as hypotonic salt solution.
3. *The Chemical*, such as saponin solutions.
4. *The Biological*, such as various haemolytic sera.

All these methods are open to objection. Mechanical haemolysis is too crude. The biological method is too difficult, owing to the inclusion of extraneous factors which almost defy standardization. The popular physico-chemical procedure of haemolysis by means of hypotonic salt solutions has one great objection, which is found in its artificiality. Imagine a corpuscle in the blood-stream of a patient suffering from pernicious anaemia. Such a corpuscle, presumably, is fighting against a powerful poison. Imagine a protective mechanism in process of production such as will prevent or lessen the haemolysing properties of the toxin. A band of scientific workers proceed to examine this corpuscle as regards its resistance. One grinds it up with sand, another bursts it with salt solution of abnormal tonicity, a third introduces the environment of an alien serum. Results are obtained, usually differing, which pretend to demonstrate the resistance of that particular diseased

corpuscle. Can such results throw any light upon the problem? It is wished to examine a patient's blood with regard to its resisting powers against the pneumococcus; is it of any value to inject tubercle bacilli and draw deductions from the results?

It is taken for granted that the corpuscle in most diseases which show blood changes is fighting against some chemical product the origin of which is as yet unknown. Surely it is not a hypotonic salt solution. The nearer the experimental haemolysing agent approaches to the hypothetical toxin present in the blood during life, the more light will then be thrown on the problems of practical medicine in this department.

The chemical method, then, is the only one remaining in the list of haemolytic agencies tabulated above. Is there any evidence to show that this method will approach nearer to the heart of the problem?

St. Faust and Tallqvist (13) investigated the subject of the anaemia caused by the intestinal parasite *Bothriocephalus latus*. From the dried bodies of this parasite a powerful haemolytic agent was isolated. But, more interesting still, this haemolytic property was found to depend upon the oleic acid contained in the isolated substance.

Similarly Preti (12) has studied the haemolysin obtained from the parasite *Ankylostomum duodenale*. He considers that this haemolytic agent is also related to the lipid group and hence closely allied to that obtained from *Bothriocephalus latus*.

These two instances, which belong to that exceedingly small group of isolated haemolysins producing anaemia *in vivo* under what may be called natural circumstances, go a long way to show the value of using this chemical method in the investigation of corpuscular fragility and its variations in diseased conditions, more especially perhaps in the anaemias. It would appear, then, that the chemical method, so far as our knowledge has progressed up till now, is the method of choice because it is the nearest approach to the condition obtaining in pathological haemolysis.

It may be mentioned here that sodium oleate was used in some experiments as a laking agent, but the permanent opalescence produced by this substance interfered with the correct observation of the results. Saponin was chosen as the best haemolytic agent and was used throughout this work. The results with sodium oleate agree in the main with those obtained with saponin.

Some work done by McPhedran (7), and published after the greater part of this work was completed, is worthy of quotation. From his researches he concludes that 'the idea that toxic haemolysis, in disease, in poisoning by phosphorus or toluene-diamine, results from the liberation of specially haemolytic fatty acids from the fatty complexes of disintegrating cells is not well supported by evidence; none of the fatty acids, still less any of the fatty complexes from which these acids can be obtained in any of the organs examined, either in this work or in the work of others that has preceded it, show on analysis any evidence for the existence of fatty acids more toxic than the

common oleic acid which is constantly being set free by hydrolysis from common fat in health'.

These conclusions do not necessarily negative the work of St. Faust and Tallqvist (13), because under normal conditions oleic acid may never be present in the blood as such, or, if present, there must be some mechanism preventing its action upon the red blood corpuscles. Perhaps in the parasitic anaemias such a mechanism is deficient.

#### *Experimental Methods.*

It is not necessary to discuss the interesting subject of the mechanism of saponin haemolysis. For those desirous of further acquaintance with recent research the admirable paper by Stewart (15) should be consulted. Suffice it to say that the saponin probably attacks the lipoid substances (lecithin, cholesterin) in the corpuscular envelope and allows the contained haemoglobin to escape.

Saponin haemolysis can be studied according to three methods:

1. The method of incubating varying amounts of saponin with the corpuscles for a certain fixed time, then reading off the results as to whether haemolysis has taken place in that time. This is the method employed by Simon, Melvin, and Roche (14). In passing, it may be stated that these observers found no alteration in corpuscular fragility in any pathological conditions.

2. The method of using always a known number of red blood corpuscles and counting the number remaining after haemolysis has taken place for a certain length of time, the results being expressed as percentages. This method was used by McNeil (6).

3. The last method is one introduced for the purposes of this work. It will be seen that the above methods observe only the result of the action of so much saponin on so many corpuscles; in fact they are statical methods. The rate of haemolysis has not been determined, therefore this last or dynamic method appears worthy of investigation.

In the earlier portion of this work the difference in time was noticed between the laking of my own corpuscles and of those in the case under investigation, both being under the same conditions in every way. This method gave results as follows:

#### *'Normal' Red Blood Corpuscles.*

1. Adult male	.	.	.	.	.	.	6 minutes.
2. " "	.	.	.	.	.	.	6½ "
3. " "	.	.	.	.	.	.	6 "
4. " "	.	.	.	.	.	.	6 "

The normal, therefore, with the concentration of saponin used is about 6 minutes.

*Experiments with Pathological Red Blood Corpuscles.**A. Splenic Anaemia.*(On different occasions)  $9\frac{1}{2}$  minutes. $10\frac{1}{2}$  „

10 „

 $9\frac{3}{4}$ *B. Pernicious Anaemia.*(On different occasions)  $7\frac{1}{2}$  minutes. $7\frac{1}{2}$  „

11 „

*C. Secondary Anaemia.*(On different occasions)  $10\frac{1}{2}$  minutes.

11 „

11 „

The objection to this method is that after a certain number of readings have been taken it becomes impossible to say when complete laking has taken place, on account of the memories of previous experiments interfering with the judgement.

This method was abandoned and the following one instituted. It has worked very successfully and has been used throughout this work.

*Technique.*

A saponin solution of 1 in 1,000 strength was made up with normal saline solution; this was kept as stock and renewed on one occasion during the work. For use, 5 c.c. of this saponin solution were diluted with 45 c.c. of saline and placed in a burette. Thus the strength of saponin actually used was 1 in 10,000 dilution.

The blood was collected in the wards of the Royal Infirmary, Liverpool, as follows: A rubber band was used to constrict the finger and a few drops of blood allowed to flow from a needle prick into tubes containing normal saline mixed with sufficient quantity of a citrate to prevent clotting and maintain the correct tonicity of the solution. My own blood was drawn off and similarly treated at the same time in every experiment. This suspension of red blood corpuscles was then centrifugalized for 10 minutes and the supernatant fluid poured away, the resulting corpuscles being regarded as 'washed'. This washing was quite sufficient, because, as experiments showed, centrifugalizing for half an hour with the citrated saline fluid renewed three times, made no difference in the results.

When the patient's corpuscles in contact with the serum were examined the blood was drawn up into a Zeiss white corpuscle counting pipette (up



to the second division on the tube) and the contents transferred to small tubes (those used in the final experiment) filled with an amount of saline solution such that when the saponin solution is added later on the total bulk will be 3 c.c.

When the patient's serum alone was required, free from red blood corpuscles, the blood was collected in Wassermann tubes. These were centrifugalized, then placed in an incubator at 37° C. for half an hour to shrink the clot, and then were centrifugalized again. The resulting serum was drawn off by a similar Zeiss pipette, only this time up to division 1 on the scale.

Reference to Plate 27, Fig. 1, is necessary to explain the remaining part of the procedure. The row of tubes in stand A are placed upon a white porcelain plate and contain saponin solution varying in amount from 1.4 c.c. to 0.4 c.c. (the range of this scale can be increased or decreased as occasion demands). The saponin solution is measured from a burette, the annoying frothing being inhibited by a drop of ether poured into the top of the burette. The tubes in row B are filled with normal saline from a burette in such quantities that the contents of each tube when added to that in its fellow in row A will make up a total volume of 3 c.c.

1.2 c.c. of saponin is regarded as the standard, and therefore the tubes containing the abnormal red blood corpuscles to be tested will also have 1.2 c.c. of saponin added to them. The reason for fixing this standard at 1.2 c.c. of saponin is solely for the sake of convenience; normal corpuscles laking with this amount of saponin in about four minutes. It will be obvious that if corpuscles so treated lake more rapidly than normal ones they will be less resistant, while corpuscles requiring a longer time to lake with 1.2 c.c. of saponin will be more resistant. In the former case the figure for the fragility will be above 100, in the latter below 100 (see Table). Into the tubes in row B the red blood corpuscles are placed, in each tube an amount of corpuscle suspension equivalent to three divisions of a Zeiss white corpuscle counting pipette. For example, in an experiment the normal scale was made up of five tubes containing my own red blood corpuscles and three tubes containing possibly abnormal red blood corpuscles. The tubes forming the scale will contain respectively 1.6 c.c. of saline corresponding with 1.4 c.c. of saponin; 1.8 c.c. saline with 1.2 c.c. saponin; 2.0 c.c. saline with 1.0 saponin; 2.2 c.c. saline with 0.8 c.c. saponin; 2.4 c.c. saline with 0.6 saponin. The tubes containing the abnormal red blood corpuscles all contain 1.8 c.c. saline and 1.2 c.c. saponin. Thus the bulk in each tube is made up to 3 c.c. total fluid.

To make an experiment the contents of each of the tubes in row B are poured into its fellow in row A, working from left to right. Having done this the tubes in row A are shaken in the reverse order, beginning at the extreme right-hand tube. Thus the time lost between the complete mixing of the first and last tube is negligible.

It will be noticed that the scale of tubes containing normal red blood corpuscles lake one after the other in regular sequence. The tubes containing abnormal red blood corpuscles are matched against the scale and one found with

which there is exact coincidence. The amount of saponin in the normal tube which corresponds to the tube under experiment is noted (say 1.2 c.c. saponin), and from the table to be described an absolute figure can be arrived at.

It should be noted that the interval between the laking of the contents in the various tubes becomes greater as the scale is traversed in a descending direction. Another point is that sometimes the 'abnormal' tube does not match any one of the normals; it is between, say, 1.2 c.c. of saponin and 1.0 c.c. of saponin. It should then be read as 1.1 c.c. of saponin and the absolute figure derived from the table as before.

One more most important practical point must be mentioned, viz. the method of matching the tubes. For the greater part of this work the tubes were placed in the stand in a direction sloping away from the observer, the eye thus looking through the contents of the tube against the white porcelain plate. Generally this method was quite satisfactory, but at times, especially when dealing with corpuscles of a very low haemoglobin content, there was some little difficulty. Undoubtedly the best way is to slope the tubes towards the observer so that the eye looks down through the aperture of the tube. At first the fluid is perfectly opalescent, then as laking proceeds one or more rings formed by the distorted image of the tube's lower end appear (Fig. 2). These rings finally become crystal clear, and the rate of laking can be watched exactly. It is best to have a strong electric light arranged behind the tubes and the glass must be kept clean. The tubes must be mixed gently or the frothing on the surface of the liquid prevents a clear view of the process.

#### *Method of expressing Results.*

The table is made up as follows:

1.2 c.c. of the saponin solution is taken as the standard and the tube containing this quantity is written down as 100. The figure 1.2 c.c. is only taken as a standard for the sake of convenience; it has no other significance. Now if one of the bloods under examination laves at the same rate as this standard it also will be 100 and therefore normal. Figures above or below this standard can be obtained by the following formula:

$$\text{Fragility of corpuscles} = \frac{x \times 1000}{12},$$

where  $x$  = the strength of saponin in the tube the haemolysing rate of which corresponds to the one under consideration.

Thus if the abnormal blood haemolyses at the same rate as the tube on the scale containing 0.8 c.c. of saponin, then  $\frac{0.8 \times 1000}{12} = 66$ .

It should be mentioned here that results above 100 may be described as 'increased fragility' or as 'diminished resistance'; similarly, results falling below 100 show either 'diminished fragility' or 'increased resistance'.

TABLE.

<i>Scale for Red Blood Corpuscles.</i>	<i>Scale for Serum.</i>
1·8 c.c. saponin = 149 . . . . .	= 116
1·7 " " = 141 . . . . .	= 108
1·6 " " = 133 . . . . .	= 100
1·5 " " = 124 . . . . .	= 92
1·4 " " = 116 . . . . .	= 84
1·3 " " = 108 . . . . .	= 76
1·2 " " = 100 . . . . .	= 68
1·1 " " = 92 . . . . .	= 60
1·0 " " = 83 . . . . .	= 52
0·9 " " = 75 . . . . .	= 44
0·8 " " = 66 . . . . .	= 36
0·7 " " = 58 . . . . .	= 28
0·6 " " = 50 . . . . .	= 20
0·5 " " = 42 . . . . .	= 12
0·4 " " = 34 . . . . .	= —
0·3 " " = 26 . . . . .	= —

The second column in the table is used for those cases in which the red blood corpuscles are examined in contact with the serum. It was found only after this work was nearly half completed that with serum the former standard of 1.2 c.c. saponin brought the reading of the fragility so low on the scale that it became necessary to make 1.6 c.c. of saponin the normal in these cases for the sake of convenience and possibly for greater accuracy.

The advantages of this method are many. The normal blood is always from the same person—myself. From the moment of withdrawing normal and pathological bloods from the body they are subject to exactly similar conditions. The temperature will be the same for both. They are washed for the same time with the same amount of citrate saline fluid. Again, the time for an experiment is short (a little over half an hour) and the apparatus such as is found in any laboratory and well-equipped hospital clinical room.

It should be remembered that another great reason why saponin is a good haemolysing agent for this work is that it does not show the phenomenon discovered by MacLean and Hutchison (8) and called by them the 'haemolytic paradox'. Some haemolysing agents such as hederin (obtained from ivy) and bile salts do not show a regular increase in haemolysing power as their concentration is increased. On the contrary, up to a certain point the more haemolysing agent is added the less is the amount of haemolysis taking place. Saponin does not show this phenomenon.

There is one possible source of error in the above method which should be mentioned. It is well known that when the rate of a chemical reaction is estimated the mass of the reacting substances must be reckoned with. Now the emulsion of red blood corpuscles in this work is made by simply pouring off the supernatant fluid. It is obvious, therefore, that the strength of this emulsion, though measured quantities of it are always used, will not always be exactly the

same. Experiments were instituted to ascertain how much this possible error affects the results. It was found that when a comparatively great increase in corpuscles was present there was a delay in haemolysis due to the increased mass of one of the reagents; but when the increase in the number of the red blood corpuscles was only slight the difference in haemolysing rate was negligible. The differences which occur in practice fall in this latter category and are negligible. Still, any divergence of corpuscular fragility less than ten must be neglected.

### *Experimental Results.*

A. *Physiological conditions.* The corpuscles are found by nearly all observers using any of the above methods to be extremely uniform in their fragility, under normal conditions. Below are given some results of saponin experiments with healthy corpuscles:

1. Healthy adult male	= 100	4 weeks later = 100
2. " " "	= 100	
3. " " "	= 100	
4. " " "	= 100	
5. " " "	= 92	
6. " " female	= 92	
7. " " "	= 83	1 day later = 92
8. " " "	= 83	3 days later = 100

Thus the normal fragility is practically constant. The slight variation in two of the female cases was probably due to some slight error in technique in one experiment.

The red blood corpuscles of certain common animals were investigated in the same manner:

1. Rabbit	red blood corpuscles	. . . .	= 133
2. Rat	" " "	. . . .	= 165
3. Guinea-pig	" " "	. . . .	= 92
4. Hen	" " "	. . . .	= 50
5. Chicken	" " "	. . . .	= 42
6. Duck	" " "	. . . .	= 42
7. Sheep	" " "	. . . .	= below 34
8. Pig	" " "	. . . .	= 58

These results show a great difference in the corpuscular fragility of the various common animals.

No reference has been found to similar experiments in the literature of haemolysis, but Dr. Wilson in the course of some work done at Liverpool (as yet unpublished) finds that the corpuscles of animals haemolyse in a similar manner with bile salts as they do with saponin.

*The Action of some common Gases upon Red Blood Corpuscles.*

It might be expected that the haemoglobin molecule with the addition of such gases as carbon monoxide would show some difference in its laking capacity or its disruption from the red blood corpuscles.

Peyton Rous (11), using a specific haemolysin, found no alteration in corpuscular fragility in cases of coal-gas poisoning. Butler (1), with hypotonic salt solution, found that oxygen decreases the fragility of red blood corpuscles to a slight extent, while carbon dioxide increases it.

Experiments were performed with pig's corpuscles which were well washed to prevent the frothing which occurs when gases are bubbled through albuminous fluids. The gases were passed into a corpuscular suspension for about three minutes :

1. Normal pig red blood corpuscles . . . . .	= 58
2. With oxygen . . . . .	= 66
3. With carbon dioxide . . . . .	= 75
4. With coal gas . . . . .	= 66

The only variation of note is the slight increased fragility of the corpuscles treated with carbon dioxide.

*Results with Normal Serum.*

The constancy of the normal figure for corpuscular fragility is not found when the additional factor of the serum is brought into the operation. Below are given some results using the 1.6 c.c. of saponin solution as 'normal', not 1.2 c.c. as in the case of washed corpuscles alone. On this scale the normal would be 133, not 100 (see table). The figures show the corpuscular fragility with the serum of the same individual also present :

1. <i>Healthy Male</i>	March 9 . . . . .	= 76
	" 10 . . . . .	= 76
	" 11 . . . . .	= 76
	" 12 . . . . .	= 44
	" 13 . . . . .	= 68
	April 23 . . . . .	= 76
	" 24 . . . . .	= 92
2. <i>Healthy Male</i>	March 10 . . . . .	= 76
	April 24 . . . . .	= 84
3. <i>Healthy Male</i>	March 10 . . . . .	= 76
	April 24 . . . . .	= 84
4. <i>Healthy Male</i>	March 10 . . . . .	= 76
	April 24 . . . . .	= 92
5. <i>Healthy Male</i> . . . . .		= 92
6. <i>Healthy Male</i> . . . . .		= 60
7. <i>Healthy Male</i> . . . . .		= 76
8. <i>Healthy Male</i> . . . . .		= 76

9. <i>Healthy Female</i>	March 9	.	.	.	.	.	.	= 68
	" 12	.	.	.	.	.	.	= 44
	April 24	.	.	.	.	.	.	= 76
10. <i>Healthy Female</i>	March 9	.	.	.	.	.	.	= 76
	" 10	.	.	.	.	.	.	= 76
	April 24	.	.	.	.	.	.	= 92
11. <i>Healthy Female</i>	.	.	.	.	.	.	.	= 36
12. Red blood corpuscles of male 1 + serum of male 2	.	.	.	.	.	.	.	= 68
13. " " " male 1 + " female 2	.	.	.	.	.	.	.	= 60

This antihaemolytic property of the serum is shown more clearly by using 1.2 c.c. of saponin solution as normal, and not 1.6 c.c. as in the above results; then

Red blood corpuscles washed	.	.	.	.	.	.	.	= 100
" " " + serum	.	.	.	.	.	.	.	= 66, sometimes 58,

showing an increase in resistance varying between 34 per cent. and 42 per cent.

At once two facts will be obvious: (1) the marked protective action which the serum exerts against haemolysis; (2) the great variation in this resistance among healthy individuals. This variation alters from day to day in the same individual and appears to have escaped the notice of previous observers. The explanation of this phenomenon appears to lie in the variation in the amount of fat present in the serum, because the naked-eye appearance of the serum continually showed variations in colour and consistency, at times golden yellow, at others milky white. The results obtained with the serum of diabetic patients would seem to support this view.

The protective action of the serum has been observed before, and experiments have been carried out to ascertain wherein lay this resistance. Simon, Melvin, and Roche (14) have shown that the chief part in the antihaemolytic powers of the serum is played by cholesterol. Following up this work, it seemed probable that by injecting an animal with cholesterol an increase in corpuscular resistance would be noted. The rat was chosen as a convenient animal, since it had a very high corpuscular fragility.

*Rat 1.* Injected subcutaneously with 0.01 grm. of cholesterol emulsified in saline, to which a small quantity of alcohol was added.

Corpuscular fragility before injection = little faster than 165.

" " 2½ hours after injection = no change.

" " 3 days " " = 165.

*Rat 2.* Treated as before. 0.005 grm. cholesterol injected.

Corpuscular fragility before injection = little faster than 165.

" " 1½ hours after injection = unchanged.

" " 3 days " " = 165.

As far as these experiments go they show only a negative result. The serum of the rats was not examined because the variations mentioned above are so misleading.



*Corpuscular Fragility under Pathological Conditions.*

I. *Jaundice.* Butler (1) gives references to many observers who have studied the corpuscular fragility in this condition, together with his own results. All these observers have found that, using hypotonic saline solution, the fragility of the corpuscle is decreased or its resistance is increased. As Butler (1) points out, this is only the case with obstructive jaundice; in congenital family cholaemia, however, he found that the corpuscular fragility was greatly increased, due, in his opinion, to some defect in the structure of the cell.

M'Neil (6), on the other hand, working with saponin, found a marked increase in the fragility of the corpuscles in obstructive jaundice, the fragility increasing with the depth of the jaundice. Peyton Rous (11), working with a specific haemolysin, found that in some cases of obstructive jaundice the resistance of the red blood corpuscles was lowered.

Two cases of obstructive jaundice were examined in this work, one particularly thoroughly.

*Case I.* Male. Suffering from cirrhosis of the liver. Jaundice very deep. This patient's red blood corpuscles were examined on many occasions and gave always the same figure, 141, which shows a marked increase in fragility. The saline fluid in which the corpuscles were washed being coloured greenish yellow from the presence of bile, it was thought that this might account for the result. Accordingly the red blood corpuscles were treated with three changes of saline solution and centrifugalized for half an hour, but they always gave the same figure, 141.

Still more interesting results were obtained when the corpuscles were examined in contact with their serum. Under these conditions the red blood corpuscles showed a marked and constant increase in resistance, viz. a figure markedly less than 34, the normal being about 66 (old scale, see introduction).

This work shows then that the washed red blood corpuscles in obstructive jaundice are more fragile than normal, while in contact with the serum they are very markedly resistant.

Experiments show that the serum from this case protects normal corpuscles in nearly the same marked way as it does its own corpuscles. The reverse experiment of treating jaundice red blood corpuscles with normal serum shows that the latter protects the corpuscles only to a normal extent.

It would appear, therefore, that the bile salts present in the serum in some way inhibit the action of the saponin. Moore, Wilson, and Hutchinson (9) found that two dissimilar haemolysing agents balance one another, while similar ones show an additive effect. Experiments were instituted to ascertain the value of this possible explanation. Varying quantities of  $\frac{M}{10}$  ox bile in saline were added to the saponin solution before the addition of the normal red blood corpuscle saline suspension, with the following results:

- |    |                                 |                              |                            |
|----|---------------------------------|------------------------------|----------------------------|
| 1. | 1.2 c.c. saponin with 0.01 c.c. | $\frac{M}{10}$ ox bile salt, | corpuscular fragility = 58 |
| 2. | 1.2 " " " 0.02 " " " "          | " " " "                      | = 58                       |
| 3. | 1.2 " " " 0.03 " " " "          | " " " "                      | = 58                       |
| 4. | 1.2 " " " 0.04 " " " "          | " " " "                      | = 58                       |

Also 5. Washed jaundice red blood corpuscles + 0.02 c.c.  $\frac{M}{10}$  ox bile salt = 100.

The first four experiments show that bile salts do antagonize the action of saponin, but not to such an extent as jaundice serum. It may be that the protective property of the latter depends upon something more than the mere presence of bile salts, because, *a priori*, if there were not some protective mechanism present in the body, then patients afflicted with even catarrhal jaundice would be expected to die from the excessive blood destruction which would certainly take place if the experiment were to be performed *in vitro*. This assumption of a more complicated protective mechanism is suggested also by the fifth experiment of the series, in which by the presence of bile salts the fragility is decreased from 141 to 100, but not to below 34, as it is by the serum.

Some nine months after the above observations the same patient came back to hospital, but this time the jaundice had completely disappeared. The corpuscular fragility was estimated and found to be 100, that is, with the disappearance of the jaundice, the fragility fell from 141 to normal (100).

*Case II.* Male. Carcinoma of stomach. Secondary nodules in the liver. Jaundice fairly well marked.

Corpuscular fragility = 124.

II. *Anaemia.* Butler (1) only examined one case of chlorosis and found practically the same result as Limbeck (5), viz. no appreciable difference in fragility. These observers used hypotonic laking agents.

A. *Chlorosis.* Five cases of *chlorosis* have been examined.

1. *Female*, aged 17. After two weeks' treatment with iron, which raised haemoglobin percentage from 55 to 70.

Feb. 20. Washed red blood corpuscles . . . = 66.

Feb. 23. " " " " " " " " = 66.

2. *Female*, aged 26. Haemoglobin 60 per cent. Reds 4,800,000.

Washed red blood corpuscles . . . = 66.

3. *Female*, aged 22. Reds 2,000,000.

Washed red blood corpuscles . . . = 66.

4. *Female*, aged 16. Reds 2,800,000. Haemoglobin 35 per cent.

Washed red blood corpuscles . . . = 83.

5. *Female*, aged 17. Reds 5,000,000. Haemoglobin 40 per cent.

Washed red blood corpuscles . . . = 66.

These results show that in this condition there is an increase in corpuscular resistance of a degree which is striking.

B. *Pernicious Anaemia.* Workers with hypotonic salt solution find no difference in this condition. Peyton Rous (11) with haemolytic serum found no lowering of resistance, nor did M'Neil (6) using saponin.

Six cases have been examined.

1. *Male*, aged 55. Reds 1,800,000. Haemoglobin 40 per cent.

Colour index 1.6.

Washed red blood corpuscles . . . = 100.

2. *Female*, aged 40. Reds 2,700,000. Haemoglobin 60 per cent.  
Colour index 1.2.  
Washed red blood corpuscles . . . . . = 108.
3. *Female*, aged 42. Reds 560,000. Haemoglobin 20 per cent.  
Colour index 1.82.  
Washed red blood corpuscles . . . . . = 100.
4. *Male*, aged 24. Reds 1,600,000. Haemoglobin 30 per cent.  
Colour index 0.9.  
Washed red blood corpuscles . . . . . = 108.
5. *Female*, aged 48. Reds 700,000. Haemoglobin 20 per cent.  
Colour index 1.43.  
Washed red blood corpuscles . . . . . = 108.
6. *Female*, aged 45. Reds 1,187,000. Haemoglobin 30 per cent.  
Slightly jaundiced.  
Washed red blood corpuscles . . . . . = 116.

It is noticed that though there is an extreme grade of anaemia in these cases they all show a normal or slightly increased corpuscular fragility. In the slightly jaundiced case the figure is higher, as might be expected.

C. *Secondary Anaemia*. In this condition McNeil (6), using saponin, found the corpuscular resistance lowered, while Peyton Rous (11), using a specific haemolytic serum, found no change in the majority of cases.

Four cases were examined.

1. *Male*, aged 45. Carcinoma ventriculi.  
Feb. 20. Washed red blood corpuscles . . . . . = 66.  
May 7. " " " " " " " " = 75.
2. *Male*. Carcinoma ventriculi.  
Washed red blood corpuscles . . . . . = 83.
3. *Male*. ? Malignant disease of lung.  
Washed red blood corpuscles . . . . . = 100.
4. *Female*, aged 23. Ulcerative colitis.  
Washed red blood corpuscles . . . . . = 83.

These results show in three of the four cases a slight increase in corpuscular resistance, but, as might be expected from the numerous causes of secondary anaemia, there is no marked uniformity.

D. *Splenic Anaemia*. McNeil (6) has shown that in this condition the corpuscular resistance to saponin is lowered. One case was examined in some detail in this work.

*Male*, aged 23. Three years' history of anaemia. Spleen enlarged. On Dec. 14, 1912, red cells were 1,600,000 and haemoglobin 34 per cent. Jan. 7, 1913, red cells 2,950,000, haemoglobin 32 per cent. The patient was treated with arsenic and salvarsan. On March 2, 1913, reds 3,000,000, haemoglobin 30 per cent.

Feb. 20, 1913.	Washed red blood corpuscles	. . . . .	= 66
Feb. 22, "	" " " "	" . . . .	= 58
Feb. 23, "	" " " "	" . . . .	= 58
Feb. 24, "	" " " "	" . . . .	= 58
Mar. 4, "	" " " "	" . . . .	= 58
Mar. 6, "	" " " "	" . . . .	= 66

Experiments with the serum of this patient were performed :

Feb. 24.	Splenic anaemia	red blood corpuscles + splenic anaemia serum	= 58
Mar. 4.	Splenic anaemia	red blood corpuscles + splenic anaemia serum	= 54
Mar. 6.	Splenic anaemia	red blood corpuscles + splenic anaemia serum	= 58

It is seen that the corpuscular resistance in this case of splenic anaemia is lowered and that, more striking still, the serum has no protective action, the corpuscles haemolysing at the same rate both with and without it.

This is the only case in this work which showed a serum with this lack of protection against saponin haemolysis. Experiments also showed that the serum of this patient protected my own corpuscles normally, and that my own serum was able to confer a degree of protection over the red blood corpuscles from the splenic case.

*E. Banti's Disease.* Male, aged 48. Enlarged liver and spleen. Slight icteric tinge.

Washed red blood corpuscles . . . . . = 75.

The slight degree of jaundice probably caused the above figure to be higher than expected.

*F. Lymphadenoma.* Washed red blood corpuscles . . . = 83.  
There was a slight grade of anaemia present in this case.

Throughout this work it has been found in all cases, with one exception, that where the number of the red cells is reduced the corpuscular resistance is increased. The one exception is pernicious anaemia. Viewed from an *a priori* standpoint, it might be said that in all cases of anaemia the corpuscles would be abnormally fragile because they are either inherently weak or under the influence of some strong destructive agent. But this *a priori* assumption appears to be wrong. The fact that in most anaemic conditions the corpuscles show an increased resistance might be accounted for by one of two hypotheses. (1) Since the erythrocytes are being destroyed in the body it is fair to assume that the weakest ones will be destroyed first. So it happens that the corpuscles examined in anaemic cases are those that have survived. (2) The more probable hypothesis is that in fighting some unknown haemolytic agent the body organizes a defensive mechanism which is localized in the corpuscles themselves. Corpuscles so endowed might be supposed to show an increased resistance to a laking agent like saponin. If a case of progressive anaemia were to be examined from its very beginning, it is conceivable that the corpuscles would show an increasing resistance up to a certain point and then become fragile owing to the defensive mechanism being exhausted.

In pernicious anaemia the corpuscles show a practically normal resistance. This curious fact may be due to the high haemoglobin content of the corpuscles, in some way rendering them more liable to haemolysis, or to the fact that there may be a slight haematogenous jaundice present which would raise the fragility

to an appreciable degree. It must be confessed that neither of these hypotheses is very satisfactory. The results appear to throw no light upon the controversy regarding the cause of pernicious anaemia, as to whether it be due to excessive blood destruction by a toxin derived from the alimentary tract (Hunter) or to a faulty production on the part of the bone marrow.

### III. *Other Blood Diseases.*

#### A. *Spleno-medullary Leukaemia.*

*Case I. Female, aged 27.* The white corpuscles had numbered 75,000; with arsenic and X-ray treatment the number was reduced to 11,000. Blood examined at the latter period.

Washed red blood corpuscles . . . . . = 100.

*Case II. Female, aged 48.* Reds 3,500,000. Whites 21,000.

Washed red blood corpuscles . . . . . = 66.

*Case III. Female, aged 23.* Reds 3,400,000. Whites 364,000.

Haemoglobin 48 per cent.

Washed red blood corpuscles . . . . . = 58.

*Case IV. Male, aged 42.* Reds 3,000,000. Whites 241,000.

Haemoglobin 50 per cent.

Washed red blood corpuscles . . . . . = 66.

The last three cases show a marked anaemia, and, as might be expected, the corpuscular resistance is lowered. In the first case no count of the red cells was made, but the patient was convalescent and greatly improved in general health.

*B. Polycythaemia. Female, aged 24.* Spleen and liver enlarged. Lungs and heart normal. No cyanosis, but marked suffusion of the skin.

Red cells 5,420,000. Whites 14,600. Haemoglobin 110 per cent.

Washed red blood corpuscles . . . . . = 75.

This case shows only a slight decrease in corpuscular fragility.

### IV. *Other Affections of the Spleen.*

#### A. *Splenomegaly.*

*Case I. Male.* Undiscovered cause. Blood picture normal.

Washed red blood corpuscles . . . . . = 75.

*Case II. Male, aged 34.* Blood picture resembles that of myelogenous leukaemia. Had enlarged glands all over body. Malaria and syphilis.

Reds 3,000,000. Whites 90,000. Haemoglobin 52 per cent.

Washed red blood corpuscles . . . . . = 34.

*Case III. Female, aged 42.* Liver, kidneys, and spleen enlarged, due to amyloid disease. Patient very anaemic.

Washed red blood corpuscles . . . . . = 58.

In these cases, also, those showing anaemia have increased corpuscular resistance.

B. *Splenectomy*. A large amount of work has been done upon corpuscular fragility in splenectomized animals. Pearce, Austin, and Krumbhaar (10) performed such experiments on splenectomized dogs, *in vitro* and *in vivo*, using in the former case both a specific serum and a hypotonic saline solution as haemolytic agents, while in the latter case a specific serum was used. It was shown that in splenectomized animals a larger dose of serum was required to produce jaundice than in normal animals. Also *in vitro* there was an increased corpuscular resistance in splenectomized animals. Weil (17) also quotes the work of Joannavicz and Pick (3) as showing that splenectomized animals are protected against toluene-diamine jaundice.

One case was examined of a boy, aged 7 years, whose spleen had to be removed surgically on account of an accident. (My thanks are due to Mr. Woolfenden, assistant surgeon, Royal Infirmary, Liverpool, and to Dr. Kennon for permission to investigate this case and for use of their notes.) The washed red blood corpuscles = 83. A slight increase in corpuscular resistance is shown. The serum had a marked increase in protective action.

Karsner and Pierce (4) have shown that the increased corpuscular resistance found in splenectomized dogs is probably due to the concomitant anaemia. Now in this case the day after the operation the red cells numbered 2,300,000. On the day that the corpuscular fragility was examined the red cells had increased to 4,000,000 and the haemoglobin was 83 per cent. The above result therefore appears to be in agreement with the work of Karsner and Pierce (4), because the case showed a slight grade of anaemia and a slight increase in corpuscular resistance. Unfortunately the case could only be examined once.

#### V. *Miscellaneous Cases.*

A. *Exophthalmic Goitre*. McNeil (6) has examined the blood of four patients suffering from this condition, and found a diminished corpuscular resistance. He quotes Dickson (2) as stating that in exophthalmic goitre there is an increased blood formation in the bone marrow. In this work the blood was practically normal.

1. *Female*, aged 26. 12 months' history  
Washed red blood corpuscles . . . . . = 100.
2. *Female*, aged 20. 2 years' history.  
Washed red blood corpuscles . . . . . = 108.
3. *Female*, aged 31. 2 years' history.  
Washed red blood corpuscles . . . . . = 100.
4. *Female*, aged 25. 10 years' history.  
Washed red blood corpuscles . . . . . = 100.

B. *Diabetes*. In this condition Butler (1) examined nine cases and found practically no change in corpuscular fragility. McNeil (6) examined four cases and found an increased resistance in three. Seven cases were examined.



1. *Female*, aged 23. March 7, 1912. 692 gr. sugar per diem. Acetone and diacetic acid in urine.

Washed red blood corpuscles . . . . .	= 100.
In presence of serum . . . . .	= less than 34.
March 10. Washed red corpuscles . . . . .	= 92.
In presence of serum . . . . .	= 28.

March 12. Normal red blood corpuscles + diabetic serum . . . . . = less than 20.

2. *Male*, aged 23. About 1,000 gr. sugar per diem. Acetone always present in urine. Diacetic acid sometimes.

Washed red blood corpuscles . . . . .	= 100.
+ Diabetic serum . . . . .	= much less than 30.
Diabetic serum + normal red blood corpuscles . . . . .	= much less than 30.

3. *Male*, aged 32. About 600 gr. sugar per diem. Acetone and diacetic acid rarely present.

Washed red blood corpuscles . . . . .	= 116.
Red blood corpuscles + diabetic serum . . . . .	= 44.
Normal red blood corpuscles + diabetic serum . . . . .	= 28.

4. *Female*, aged 51. 814 gr. sugar per diem. Trace of acetone. No diacetic acid.

Washed red blood corpuscles . . . . .	= 82.
Normal red blood corpuscles + diabetic serum . . . . .	= 68.

5. *Male*, aged 55. 16 years' history. About 1,000 gr. sugar per diem. No acetone or diacetic acid.

Washed red blood corpuscles . . . . .	= 82.
Red blood corpuscles + diabetic serum . . . . .	= 60.

6. *Female*, aged 15. 200 gr. sugar per diem. Acetone and diacetic acid usually present.

Washed red blood corpuscles . . . . .	= 82.
Red blood corpuscles + diabetic serum . . . . .	= 36.

7. *Female*, aged 50. Sugar 4.4 per cent. per diem. Acetone and diacetic acid present.

Washed red blood corpuscles . . . . .	= 81.
Red blood corpuscles + diabetic serum . . . . .	= 68.

To sum up these results, four cases show an increased corpuscular resistance, two are normal, and one shows a diminished resistance. These figures can be accounted for by the slight grade of anaemia present in some of the cases.

The interesting feature is the increase in the protective power of the serum shown in some of the cases, especially over normal corpuscles. This fact can be explained by assuming that in these cases a lipaemia was present, the fat in the serum combining with some of the saponin. It must be admitted, however, that the serum did not show a lipaemic condition to the naked eye.

C. *Scurvy*. *Male*, aged 44. Red cells 3,000,000. Whites 12,500.

Washed red blood corpuscles . . . . .	= 83.
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This increased resistance can be accounted for by the concomitant anaemia.

D. *Paroxysmal Haemoglobinuria*. Butler found a normal fragility in this condition.

*Male*, aged 24. Blood examined at termination of attack.

Washed red blood corpuscles . . . . .	= 100.
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It will be seen that this result agrees with Butler.



3. The corpuscles of various animals show marked variation in their fragility.
4. In jaundice the resistance of the washed red blood corpuscles is markedly diminished, while the protective action of the serum is markedly increased. This latter result is not due only to the antagonistic action of saponin and bile salts.
5. In all the anaemias, except pernicious anaemia, the corpuscular resistance is increased. In pernicious anaemia it is normal or slightly diminished. In splenic anaemia there is great increase in corpuscular resistance, and the serum appears to have no protective reaction.
6. In the anaemia found in malignant disease, syphilis, tuberculosis, scurvy, amyloid disease, and myelogenous leukaemia, and in a case of splenectomy there was an increased corpuscular resistance.
7. In diabetes the corpuscular fragility is normal, while the serum in some cases is abnormally protective.
8. In exophthalmic goitre and paroxysmal haemoglobinuria the corpuscular fragility is normal.
9. In polycythaemia the resistance is increased.
10. A high temperature appears to increase corpuscular fragility.

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My thanks are due to the Honorary Physicians of the Royal Infirmary, Liverpool, for permission to examine the cases under their care, to Professor Moore and Dr. Wilson for help in the theoretical aspects of this work, and to Mr. Webster for much practical assistance in the laboratory.

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## DESCRIPTION OF PLATE.

PLATE 27, FIG. 1. Drawing from a photograph of an actual experiment just prior to mixing of the tubes. On this occasion the possibly abnormal bloods belonged to a laboratory colleague, a pig, and a rat respectively.

FIG. 2. Shows drawings of photographs taken during the course of an experiment upon the fragility of sheep's corpuscles. In the top drawing two tubes are seen containing equal quantities of saponin and saline corpuscular emulsion. The left-hand tube contains normal human red blood corpuscles; the right-hand tube, sheep's red blood corpuscles. The top drawing is at the commencement of the experiment when tubes show opalescence.

The second drawing shows the same two tubes after four minutes. The tube containing human red blood corpuscles has laked, as shown by the black ring; that containing sheep's corpuscles has not yet laked, and hence no ring is seen.

The last drawing shows, by the presence of the ring in the right-hand tube also, that the sheep's corpuscles have undergone haemolysis. Such a result takes considerably over an hour for its completion. It is obvious, then, that sheep's red blood corpuscles are more resistant to saponin than are human red blood corpuscles.

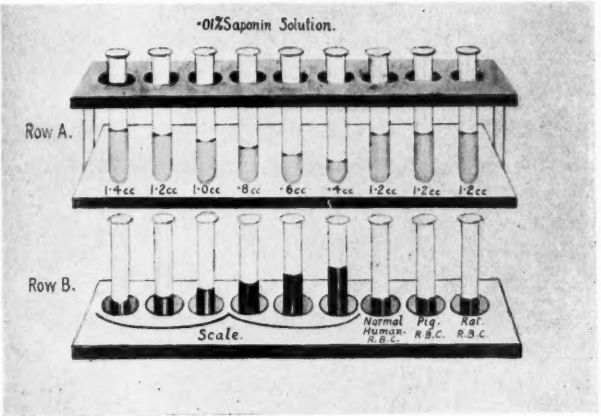


FIG. 1

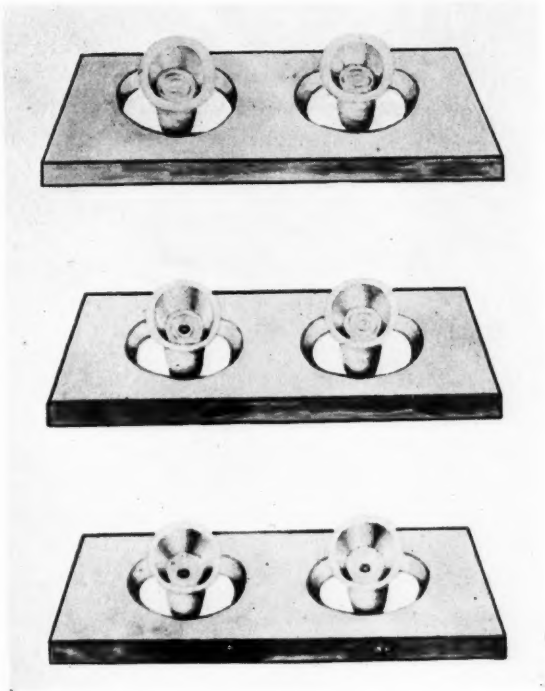


FIG. 2





## STUDY OF A CASE OF VERY PROLONGED CHEYNE-STOKES BREATHING

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With Plates 28 and 29

### *Introductory.*

ALTHOUGH Cheyne-Stokes breathing in man does not, as a rule, last long, for by the time of its onset in the maladies which it usually accompanies the patient is not far from his end, yet occasional exceptions occur. For example, it may be seen in healthy sleep especially that of infants, after certain poisons, and when the atmospheric pressure is greatly reduced as on high mountains. An anonymous writer in the *Lancet*, H. S. (1), says that his father, who died at the age of 92, had it for at least sixteen years before his death. Dixon Mann (2) records that 'I have recently had under continuous observation a case probably unique in which Cheyne-Stokes breathing lasted for more than a year'. This was a man who had extreme arterial degeneration and who was 70 years old at death. G. A. Gibson (3), who gives a very full account of the earlier literature of the subject, quotes Cuffer as saying that it may persist for years in cases of gout and renal disease, and he refers to (a) an elderly gentleman who for many years during his daily sleep after dinner breathed in a manner characteristic of Cheyne-Stokes breathing; (b) a lady whose breathing for many years was periodic during sleep. In her and her sister this had occurred since childhood. He also states that there is an inherited liability to Cheyne-Stokes breathing in some families. West (4) gives a case of granular kidney in which Cheyne-Stokes breathing lasted three months. Pitt, Pembrey, and Allen (5) have investigated a man, aged 43, who had Cheyne-Stokes breathing for ten weeks. He suffered from aortic disease. His kidneys were apparently normal, and the cerebral vessels were not specially thickened. Goodhart, Pembrey, Plumpton, and Schlesinger (18) have investigated another patient who had extensive atheroma and hyaline degeneration of the cerebral vessels. He showed Cheyne-Stokes breathing off and on for 79 days. Taylor, Pembrey, Beddard, and French (19) have investigated a man of 46 who had Cheyne-Stokes breathing for  $6\frac{1}{2}$  months. At the post-mortem small granular kidneys and a hypertrophied heart were found. In another instance the patient showed Cheyne-Stokes breathing for

several days after an injury to his head; he subsequently recovered. In some of these cases (5, 18, 19) the microscopical appearance of the various nuclei in the medulla was also investigated. Chromatolytic and degenerative changes were most marked in the dorsal nucleus of the vagus, while the hypoglossal nucleus was apparently quite healthy. Other examples of prolonged Cheyne-Stokes breathing may be found in medical literature.

The subjoined case has seemed to us worthy of record for the following reasons: (a) Cheyne-Stokes breathing lasted certainly six months, and from the account given by the patient's wife possibly for very much longer. It was present during both sleeping and waking. (b) Although the patient was, as shown by the condition of the retinae, the hypertrophy of the heart, and the high blood pressure, an example of arterio-sclerosis, yet the post-mortem examination disclosed that the arterial change was not extensive, for the arteries in the brain were normal, as were many of those in the kidneys, and these organs were not advanced beyond an early granular change. In these particulars this case resembled that described by Pitt, Pembrey, and Allen, but in most of the few recorded cases of prolonged Cheyne-Stokes breathing in patients like ours either the arterial change was severe, the granular changes in the kidneys were advanced, or the patient was aged; ours was only 42 years old. (c) The composition of the alveolar air was determined on several occasions, and it was possible to confirm the findings of previous observers. (d) Observations on the blood dissociation curve by Barcroft's method showed that the blood was abnormally acid, and we obtained proof that the respiratory centre suffered from diminished excitability. (e) Analyses of the urine and blood proved that lactic acid was not the cause of the increased acidity of the blood. (f) Histological examination of the respiratory centre showed changes similar to those already described by previous observers, although it is unfortunately at present impossible to say whether they are the result or partly the cause of the Cheyne-Stokes breathing.

#### *Clinical Notes.*

George M., shopkeeper, aged 42, a patient of my former house physician, Dr. E. Lionel Elliott, of Sevenoaks, was sent to Guy's Hospital, April 10, 1913, for admission under my care (W. H. W.). Dr. Elliott has kindly supplied me with the following history: Always a delicate child, never had scarlet fever. As far as is known, no member of his family has had similar breathing. At the age of 26, when his wife first knew him, he used to play football, but every winter had a troublesome cough with some shortness of breath which got worse every year. His wife said it gradually became of the same kind as he had had when in Guy's (Cheyne-Stokes), and that it was caused by severe exertion. On this account, for three or four years before admission he had always avoided extra exertion and had taken a cab from the station to his house when returning from London. He had taken alcohol freely. From 1906 onwards he used to go to a doctor's surgery two or three times a year for a bottle of medicine for indigestion, but during this time he had no acute illness. He first noticed swelling of the ankles in May, 1912, and in August, 1912, he first consulted Dr. Lionel Elliott. His breathlessness was then present, but he did not specially mention it as he had had it so long; he only complained of a pain in the back. Albumin (1-2 parts

per 1,000) was found in the urine. He was dieted and he improved in health for a time, but on January 20, 1913, was sent to bed on account of increasing albuminuria, swelling of the feet, and breathlessness. He was kept in bed on milk diet seven weeks and the albumin was usually about 6 parts per 1,000. He got up at the end of March and went to stay with his brother in Essex. Being worse at the end of a week, he returned to Sevenoaks, and Dr. Lionel Elliott again put him to bed. He was then very breathless and the breathing was Cheyne-Stokes; it was especially noticeable when he was flurried. He remained in bed until his admission to Guy's. During all this time his breathing was Cheyne-Stokes. His urine was scanty, but the quantity passed increased a little if diuretin was given. Albuminuria persisted. He complained much of pain in the back, sleeplessness, and loss of appetite.

*On admission.* Nothing of importance could be learned as to his family history. He was obviously in great distress from dyspnoea; so much so, that it was difficult for him to talk. The breathing was typical Cheyne-Stokes, the dyspnoea gradually waxing, then waning. Rhonchi could be heard all over the chest on both sides. The impulse of the heart was felt two inches outside the nipple line in the fifth space. The dullness was proportionately increased and the left side of the heart was obviously hypertrophied. There were no murmurs. The pulse was regular, arteries thick, blood pressure 195 mm. Hg. The umbilicus bulged and there were all the signs of considerable ascites; there was much oedema of the lower extremities. The liver was firm and was uniformly enlarged, extending to  $2\frac{1}{4}$  inches below the ribs. The urine was scanty; sp. gr. 1.020; considerable albuminuria. The diagnosis was arterio-sclerosis, granular kidney, hypertrophied heart, and uraemia. Hot-air baths, pilocarpine, hot fluids to drink, and venesection were ordered. After this treatment he vomited once, but his breathing was much easier and he felt better.

He remained in the hospital till September 2, 1913. During this time, although at first there was some improvement, he on the whole got gradually weaker. This was shown, not only in his general condition, but the heart became feebler, his pulse weaker, and the tension of it gradually got less. The only rally was in July, when for a little he got better; his blood pressure then was 180, but he soon relapsed. He was much troubled by oedema of the lower extremities, ascites, and some fluid at the bases of his pleural cavities. Various treatments were tried for this water-logging, but by far the most efficacious was acupuncture of the legs. This was done several times, much fluid always drained away; after it the oedema, ascites, and pleural effusion lessened and the patient was more comfortable. The albumin was usually between 10 and 20 parts per 1,000 and the urine was scanty. Hyaline, epithelial, and granular casts and, towards the end of the case, some pus were found constantly in the urine. There was no blood. The larynx was seen to be quite healthy by laryngoscopic examination. A Wassermann reaction was done twice and was negative on each occasion. Insomnia was a great trouble. The temperature, taken in the mouth, was always subnormal, but this did not indicate the real temperature of the body, for when taken in the axilla or rectum it was normal. The patient left the hospital at his own request on September 2, 1913.

As regards the eyes, Mr. Eason on April 25 reported: 'There is extensive arterio-sclerosis of the retinal vessels in both eyes. The arteries are small, irregular in calibre, tortuous and rigid, as is shown by the constriction of the veins where they are crossed by the arteries. Owing to the obstruction of the venous circulation by the arteries and also owing to defects in the arteries themselves there are numerous haemorrhages, both flame-shaped and petechial, in the neighbourhood of the disks. Though there is some oedema in the neighbourhood of the disks, there is no optic neuritis, as the physiological excavation of both disks is still clear. There is no alteration of the size of either arteries or veins during apnoea or dyspnoea.' On August 1, 1913,

Mr. Eason again reported: 'The general appearance of the fundus remains much the same. There are still retinal haemorrhages, petechial rather than flame-shaped in character, and some areas of retinal exudate. The outlines of the disks remain clear and there is no extravasation into the physiological cup. The arteries still compress the veins, but there is no increase in either their irregularity of calibre or tortuosity.'

After leaving the hospital the patient again passed into the care of Dr. Elliott, but he only lived five days. During this time the dyspnoea and oedema increased. There was some vomiting. The patient never became unconscious; he said inhalations of oxygen relieved him greatly. Directly death took place Dr. Elliott telegraphed to my house physician, Dr. P. W. S. George (I was away on my holiday), who at once went down with the post-mortem room assistant and removed a piece of liver, the kidneys, the brain, and the spinal cord. Unfortunately, a complete post-mortem examination was not allowed.

During his stay the following observations were made:

*Breathing.* During the whole twenty-one weeks the patient was in the hospital his breathing was Cheyne-Stokes, but its periodicity was not always equally striking. He clearly suffered very greatly from breathlessness, and it always struck us as much greater than could be accounted for by the condition of the heart or lungs. He could not lie down. Often there was no lividity, and when it was present it was slight. He always felt better for oxygen inhalations.

The length of the periods of apnoea and dyspnoea varied.

April 11. Dyspnoea period was 41 sec., with 23 respirations.

	Apnoea	"	"	32	"	
"	18. Dyspnoea	"	"	35	"	15 "
	Apnoea	"	"	22	"	
"	28. Dyspnoea	"	"	33	"	15 "
	Apnoea	"	"	15	"	
May	29. Dyspnoea	"	"	46	"	32 "
	Apnoea	"	"	25	"	
Sept.	2. Dyspnoea	"	"	65	"	
	Apnoea	"	"	25	"	

Some attention was paid to the possibility of variation of symptoms during the respiratory cycle. The patient himself, when asked, stated that he did not notice any mental changes such as have been observed in other cases. There were no 'forced movements' during dyspnoea and no alteration in muscular power—as tested by the hand grips—in any part of the cycle. One physical sign in particular was found to be variable. The plantar reflex, which was extensor, could be elicited during apnoea but not at all during dyspnoea. Cyanosis of the face, if present, began just towards the end of the apnoeic period and reached a maximum during the first half of the dyspnoeic period; it had completely disappeared by the end of dyspnoea. This is explained by the analysis of the alveolar air as described by Pembrey.

*The Composition of the Alveolar Air and the Dissociation Curve of the Blood.*<sup>1</sup>

Dr. E. P. Poulton reports as follows: Investigations by Pembrey (5) and his co-workers on Cheyne-Stokes respiration in pathological conditions have been directed towards finding out the variations in the composition of the alveolar air at different points in the respiratory cycle. The results have thrown considerable light on the cause of the periodic breathing in these conditions. Douglas and Haldane (6) have shown that the same causes underlie the varieties of physiological Cheyne-Stokes breathing which occur at high altitudes, or after prolonged periods of forced breathing.

Observations on the respiration of the present case were first carried out on April 11, soon after the patient's admission into the hospital, when he was very dyspnoeic and orthopnoeic. The Cheyne-Stokes breathing was extreme, the time of each period being 73 seconds. Dyspnoea lasted for 41 seconds, during which 23 respirations were taken, followed by cessation of breathing for 32 seconds. The actual amount of the patient's dyspnoea was estimated by Douglas's apparatus (7) for determining the total respiratory exchange in man, which is admirably adapted for clinical work. The patient breathes through a mask fitted with inspiratory and expiratory valves into a large bag, and the volume of the air collected during a given time is measured by subsequently expelling it from the bag through a gas-meter. (For results see Table I.)

The total amount of air breathed per minute was 15.6 litres measured, saturated with moisture, at the body temperature. This is considerably above the normal, which usually ranges from 5.6 to 10.8 litres per minute, though sometimes much higher volumes have been recorded in healthy subjects. The average amount of air per breath was 825 c.c., which is much above normal; but as the respirations were very shallow at the end and beginning of the dyspnoeic period the size of the middle breaths was much greater still.

The respiratory exchange was also determined. The  $\text{CO}_2$  output was 206 c.c. minute, while the oxygen intake was 290 c.c. The fact that the patient was sitting up in bed and was very dyspnoeic would account for the small increase of the figures above the normal (8). The respiratory quotient was 0.71, considerably lower than normal.

The composition of the alveolar air is shown in Table I. At the end of dyspnoea it contained 2.3 per cent.  $\text{CO}_2$  and 18.4 per cent.  $\text{O}_2$ ; at the beginning of dyspnoea it contained 4.2 per cent.  $\text{CO}_2$  and 11.7 per cent.  $\text{O}_2$ . These figures are the mean of several concordant results, obtained by collecting the sample after a forced expiration through a long tube at the beginning or end of dyspnoea. The tube was fitted with a wide-bore aluminium tap at its proximal end, which was closed immediately after the forced expiration. By this means

<sup>1</sup> The expenses of this investigation were defrayed by a Government grant from the Royal Society to Dr. Pembrey.



there was no necessity for the patient to close the end of the tube with his tongue, as described in the original Haldane-Priestley method. The results show that during dyspnoea the  $\text{CO}_2$  percentage gradually falls, and rises again during the apnoeic period. The oxygen varies in the opposite direction. The explanation of these changes that has been put forward by Pembrey and Allen (5) is that the increased ventilation during dyspnoea washes out  $\text{CO}_2$  from the lungs and raises the percentage of oxygen. During apnoea, on the other hand,  $\text{CO}_2$  gradually accumulates again, but rather slowly, owing to the washing out of the  $\text{CO}_2$  from the blood that has occurred, and during this time the oxygen falls to a value considerably below the normal value for the alveolar air. At this point the patient suffers from actual want of oxygen, as is shown by the distinct cyanosis of the face and slight cyanosis of the hands that was noticed at the end of apnoea and at the beginning of dyspnoea in our case; this cyanosis completely disappeared before the end of dyspnoea, showing that the want of oxygen had been removed.

The periodicity of the breathing is due to two independent variable factors. On the one hand, during apnoea we have the gradually accumulating  $\text{CO}_2$ ; on the other hand, we have the want of oxygen. These two factors act together in starting the breathing. During dyspnoea the want of oxygen and the accumulated  $\text{CO}_2$  is rapidly removed and so the breathing is arrested.

If the periodicity of the respiration is to be explained in this way, it will be abolished if either of these factors is done away with separately. Oxygen was administered through a mask and valves and a graphic representation of the breathing was taken by a stethograph and revolving drum. This inhalation of oxygen caused the breathing to become continuous after one minute. The effect of increasing the  $\text{CO}_2$  in the air breathed also caused the periodic breathing to disappear.

The effect of these two factors must be further considered. Under the ordinary conditions of everyday life, Haldane and Priestley (9) showed that breathing was regulated solely by the percentage of  $\text{CO}_2$  in the alveolar air, and it is now believed that it acts only in virtue of its acid character. The aerated blood that leaves the lungs is in equilibrium with the  $\text{CO}_2$  pressure of the alveolar air, and the partial pressure of  $\text{CO}_2$  in the arterial blood is actually the same as the  $\text{CO}_2$  pressure in the alveolar air. This fact has been verified by Krogh with animal experiments. It follows that a rise in the amount of  $\text{CO}_2$  in the lungs means an increase in the pressure of  $\text{CO}_2$  in the arterial blood and so an increase in the acidity of the blood, or, rather, a diminution in its alkalinity. This will occur at the end of apnoea, while at the end of dyspnoea the arterial blood will be more alkaline as the  $\text{CO}_2$  is lower.

Considerable discussion has arisen as to how the want of oxygen at the end of apnoea acts as an additional stimulus to respiration. Perhaps the most satisfactory explanation at present is that it produces an increase in the excitability of the respiratory centre, which thus reacts to a lower arterial hydrogen ion concentration than when there is no deficiency of oxygen. On



this hypothesis the periodicity is due to an acid stimulus in the arterial blood of varying intensity acting on a respiratory centre of varying excitability.

The most direct way of investigating the alkalinity or acidity of such a complex liquid as blood is to measure its hydrogen ion concentration by physical means, and this has been done by Hasselbalch (10). Any method of measuring it by titrating serum cannot give results of any value in this connexion.

There is, however, another method of measuring the relative acidity of the arterial blood apart from the complicated method described by Hasselbalch, and that is by taking advantage of a property of blood haemoglobin worked out by Barcroft. He has found that the dissociation curve of blood depends on its relative acidity; in other words, this curve can be shifted downwards or upwards by adding acid or alkali to the blood. A blood dissociation curve is the relation between the oxygen pressure and the corresponding percentage saturation of the oxyhaemoglobin with oxygen. All human dissociation curves appear to be represented by the formula of A. V. Hill (11):

$$\frac{y}{100} = \frac{Kx^{2.5}}{1 + Kx^{2.5}},$$

where  $y$  = per cent. saturation and  $x$  = oxygen pressure in millimetres, and where  $K$  is a constant, which, however, varies with the acidity of the blood, becoming smaller as the relative acidity becomes greater. This property enables us to determine the acidity (and presumably hydrogen ion concentration) of the arterial blood, that acts on the respiratory centre. A sample of venous blood is withdrawn from an individual and defibrinated. It is then exposed in a closed vessel to an atmosphere which is similar to that of the alveolar air, and rotated in a water-bath kept at the temperature of the body. By this means the venous blood has been virtually converted into arterial blood. The percentage saturation is then determined by Barcroft's (12) gas analysis apparatus. It has been found in this way that the dissociation curves of the arterial blood of normal individuals vary within rather narrow limits: i.e. the values of  $K$  vary from 0.00023 to 0.00033. In certain pathological conditions, e.g. uraemia, the arterial blood is distinctly more acid than normal. In a number of cases investigated by Lewis, Barcroft, and others (13)  $K$  varied between 0.00008 and 0.00022, and in four cases investigated by Poulton and Ryffel (14) values of  $K$  between 0.000122 and 0.000167 were obtained.

In cases of Cheyne-Stokes breathing the acidity of the arterial blood, in other words the dissociation curve, will vary with the percentage of  $\text{CO}_2$  in the alveolar air. It will be highest at the end of apnoea and lowest at the end of dyspnoea. It will be noticed from Table I that at the beginning of dyspnoea in our patient the blood was abnormally acid ( $K = 0.000157$ ), whereas the value for  $K$  was about normal at the beginning of apnoea. This proves that there was a permanent diminution in the excitability of the respiratory centre because a blood of normal acidity failed to excite any respiration at all, and a blood

of abnormal acidity ( $K = 0.000157$ ) only excited respiration when presumably the centre was over-excitabile from want of oxygen at the end of apnoea.

Pembrey (15) has pointed out that physiological Cheyne-Stokes breathing often occurs in cases in which there is diminished nervous excitability, e.g. in hibernating dormice. He has suggested that in these cases the respiratory centre is also less excitabile than usual, and has pointed to the histological changes in the vagal nuclei to support this hypothesis.

In the present instance there is definite evidence of an experimental nature that the excitability of the respiratory centre was diminished.

As a result of the venesection which took place on April 11 after the observations just mentioned, the patient improved. When investigated again on April 18 the dyspnoea was not so great; the total period of the cycle was shortened to 57 seconds. Of this the dyspnoea, consisting of 15 respirations, occupied 35 seconds, and the apnoea 22 seconds. The cyanosis at the beginning of dyspnoea was only just perceptible. The dissociation curve of the blood was redetermined on April 16, and Table I shows that it had become distinctly less acid, coinciding with the lessening of the dyspnoea.  $K$  was 0.000218 with a pressure of 29 mm.  $\text{CO}_2$ .

At the end of April the improvement of the patient's condition was still maintained. This is well shown by determination of the pulmonary ventilation on two occasions, April 28 and May 2. The values 11.1 and 11.9 litres per minute fall within normal limits. The respiratory exchange was also rather less than before, viz. 190 c.c.  $\text{CO}_2$  and 240 c.c. oxygen, the quotient being 0.8. It is interesting to note that while the pulmonary ventilation had fallen by 25 per cent., the metabolism, deduced from the respiratory exchange, was only slightly diminished; which shows the independence of these two processes. The breathing was not so deep, the average depth of a respiration being 600 c.c. The composition of the alveolar air was reinvestigated. The differences were that at the end of dyspnoea the  $\text{CO}_2$ , and at the end of apnoea the oxygen, did not fall so low as previously.

By May 29, when the patient was investigated for the last time, the weather had become much hotter and he was much more dyspnoeic. Cyanosis was again marked and the total cycle of the breathing was increased to 71 seconds.

If the present case is compared with those cases of uraemia previously investigated there are several features in common. In the first place, the alveolar  $\text{CO}_2$  values are abnormally low, 15–30 mm. instead of 40 mm. This must be due to the accumulation of fixed acids in the blood. It shows the reaction on the part of the respiratory centre to increased acidity, the object of which is to keep the body fluids as near the neutrality point as possible.

In the second place, the arterial blood is abnormally acid in reaction, except just at the beginning of apnoea. This has been shown to be due to a permanent diminution in the excitability of the respiratory centre, which only reacts to a greater acidity than normal.

TABLE I.

Date.	Pulmonary Ventilation. Litres per min. (Measured wet at 37° C. and at prevailing atmo- spheric pressure.)	Composition of Alveolar Air.				Dissociation Curves at given CO <sub>2</sub> pressures.		
		% CO <sub>2</sub> .	Mm. Hg.	% O <sub>2</sub> .	Mm. Hg.	CO <sub>2</sub> Pres- sure, mm.	% Saturation correspond- ing to 30 mm. O <sub>2</sub> .	K.
April 11	15.6	(beginning of dyspnoea) 4.2 (end of dyspnoea) 2.3	30 16	11.7 18.4	83 131	29 16	43.6 56.3	.000157 .000261
April 16	—	—	—	—	—	29	51.9	.000218
April 28	11.1	(beginning of dyspnoea) 4.3 (end of dyspnoea) 3.1	31 22	15.0 18.0	106 127	—	—	—
May 2	11.9	—	—	—	—	—	—	—
Normal man * J. B.	—	5.6	40	14.1	100 (approx.)	40	58	.000292
Limits of variations in normal subjects	10.8+	5.0	36	—	—	Alv. CO <sub>2</sub> pressure	55	.00023
	5.6	6.0	43	—	—	Alv. CO <sub>2</sub> pressure	63	.00033

\* Barcroft and Poulton, *Journ. Physiol.*, Camb., 1913, xlii, Proc. 4.+ Pembrey and Schlesinger, *ibid.*, 1908, xxxvii, Proc. 64.TABLE II. *Urine Analysis.*

Date.	Nitrogen %.	Volume c.c.	Per Diem.				In per cent. of Total Nitrogen.		
			Nitrogen grms.	Uric Acid grm.	Creatinin grm.	Ammonia Nitrogen grm.	Ammonia.	Creatinin.	Uric Acid
April 10-11	1.12	550	6.16	0.331	0.610	0.278	4.53	3.67	1.79
" 11-12	1.67	400	6.68	0.317	0.584	0.290	4.34	3.25	1.58
" 12-13	1.78	640	11.38	0.607	0.792	0.403	3.55	2.58	1.77
" 13-14	1.78	690	12.31	0.619	0.828	0.647	5.26	2.41	1.59
" 14-15	1.76	365 *	6.42	0.475	0.501	0.315	4.90	2.90	2.46
Folin's average normals on standard diet	1.12	1,430	16	0.37	1.55	0.70	4.3	3.6	0.8
Urea in blood on April 11		0.75 per 1,000					0.28 per 1,000		
" " " "		16							
" " " "		0.76							

Lactic acid in blood on April 11  
Bled on April 11 12 ozs.

The urines contained albumin from 2.5 to 7 per 1,000, were highly coloured owing to the presence of considerable amounts of urobilin, deposited large amounts of acid urate, and contained but little chloride.

\* Probably a little urine missing.

Further, it is possible that this permanently diminished excitability of the respiratory centre may also explain the acid values obtained in uraemia generally.

#### *Urine and Blood.*

Mr. Ryffel examined the urine and blood during life. The following is his report :

*Methods.* Nitrogen : Kjeldahl.

Uric acid, creatinin, acidity : Folin.

Ammonia : formalin.

Urea in blood : hypobromite after treatment with alcohol.

Lactic acid : Ryffel.

(For results see Table II.)

Urea in the blood would not normally be above 0.3 per 1,000 on the diet the patient was receiving, so that the results afford some evidence of kidney insufficiency, but the urines were concentrated, which is not usually the case in uraemia patients.

Lactic acid in the blood normally amounts to from 0.12 to 0.16 per 1,000 in people below the age of 40. At 50 and upwards amounts ranging from 0.16 to 0.36 per 1,000 have been found in apparently normal individuals, so that the lactic acid is not definitely above normal limits (Lewis and others, 13).

The output of nitrogen shows considerable variation in spite of a constant diet of three pints of milk daily. Venesection may be the cause of the subsequent increase of urinary nitrogen, but the urea in the blood was identical on the 11th and 16th, so that there is no evidence that retained nitrogen was excreted in this period. The increased output, however, of uric acid and total acid in the same period corresponds to the diminution of the acidity of the blood previously mentioned.

Folin's (16) results, which are given in the table, are for a much more generous diet. Taking this into account, however, the uric acid is clearly abnormally high and the creatinin abnormally low. The latter result corresponds with Mellanby's (17) observation that the daily output of creatinin is diminished in disorders of the liver.

#### *The Liver and Kidneys.*

Dr. R. A. Chisolm examined sections of these and reports : ' The liver shows typical nutmeg change of an advanced type (Plate 28, Fig. 1). The kidneys are rather large. The capsule strips easily. The surface is coarsely granular, but there are no cysts. The glomeruli are somewhat large. There is no thickening of Bowman's capsule and the tufts appear normal (Fig. 2). The arterial walls are thickened in places, but many of the arteries are normal in appearance. There

is a slight excess of connective tissue in the neighbourhood of some of the arteries, but most of the kidney is free from interstitial fibrosis. The epithelium of the convoluted tubes is very necrotic, the cells being ragged in appearance, and the nuclei stain badly (Fig. 3). The lumen of the tubes is filled with amorphous debris and some leucocyte casts. The straight tubules are comparatively unaffected. The kidneys have the appearance of early arterio-sclerotic change with superimposed tubal necrosis.' Both were examined; the changes were similar in each of them.

#### *The Central Nervous System.*

Dr. W. Johnson examined this and reports that the whole of the medulla and mid-brain, together with certain portions of the cerebral cortex, were received for examination. Fixation was carried out in 10 per cent. formalin.

*Macroscopical examination.* The naked-eye characters were in every respect normal. The meninges showed no thickening or other abnormal appearance. The pia-arachnoid could be stripped with ease from the surface of the brain. The vessels of the circle of Willis, together with its various branches, were of normal appearance and exhibited no thickening or atheromatous change. Special attention was given to the vessels from the basilar artery supplying the medulla, and they were found to be in a similarly healthy condition.

On cutting up the brain, pons, and medulla no gross pathological changes were to be seen.

*Histological examination.* 1. Sections were stained with haematoxylin and eosin and were studied especially from the point of view of the condition of the arteries. As the accompanying photograph (Plate 29, Fig. 4) shows, there is complete absence of any proliferation of the arterial wall, either local or general. The arteries everywhere were found to be quite normal. Their perivascular sheaths were also entirely free of any inflammatory changes.

2. Sections stained with thionin blue (Nissl modification). The object of this examination was to investigate the condition of nerve cells—especially those of the vagus centre, the so-called respiratory centre.

*Hypoglossal nucleus.* The nerve cells here stain well. The nuclei are centrally placed and Nissl's granules are large and well defined (Figs. 5 and 6). These photographs from this nucleus show three normal nerve cells.

*Eighth nerve nucleus.* These cells, somewhat smaller than the above, show an equally healthy condition.

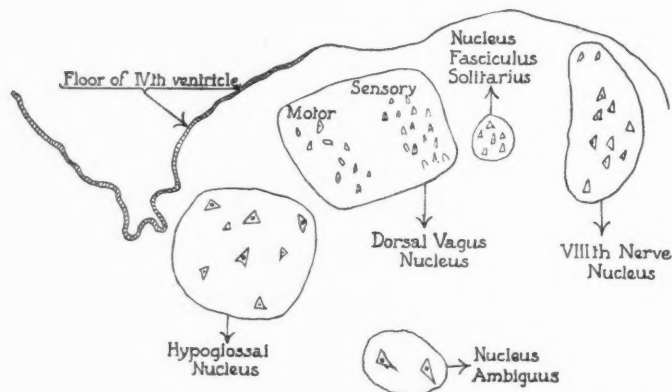
*Vagus centre.* The relation of the various groups of nerve cells forming this centre is shown in the drawing on p. 400.

(a) *Nucleus ambiguus.* The large clearly defined cells in this nucleus are well preserved and in a healthy state.

(b) *Nucleus fasciculus solitarius.* The few nerve cells present here exhibit slight chromatolysis. The nuclei tend to hold an excentric position in the cell,

and there is some diffuse staining in the cell-body due to a slight breaking up of Nissl's granules.

(c) *Dorsal vagus nucleus.* The chromatolytic changes here were extreme. Several cells were wasted and stained a dark blue; in them neither nucleus nor Nissl's granules were distinguishable. Other cells were swollen, showing an excentric nucleus and a remnant of Nissl's granules at the periphery of the cell.



No healthy cells could be seen anywhere. As regards the two groups of cells into which this nucleus is divided, it is noteworthy that a severer degree of chromatolysis was present in the outer (sensory) portion than in the inner (motor) portion. In the former group the majority of the cells showed chiefly a wasted or atrophied condition (Plate 29, Figs. 7 and 8).

*Conclusions.* The changes here described are to be regarded as evidence of exhaustion of the nerve cells in the respiratory centre. They closely resemble changes which I have observed in a large series of cases, in which death has occurred after a period of terminal dyspnoea. In the case under consideration here it has to be remembered that, in addition to the condition of Cheyne-Stokes breathing, there was also present a terminal period of dyspnoea lasting four or five days. It is exceedingly difficult, therefore, to decide how far the changes observed are directly associated with the terminal dyspnoea on the one hand, and with Cheyne-Stokes respiration on the other. My study of the respiratory centre in other conditions would appear to indicate that the terminal dyspnoea has played the greater part.



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## DESCRIPTION OF FIGURES.

PLATE 28, FIG. 1. A section of the liver. In the centre is seen the intralobular vein, and near it are groups of atrophied liver cells separated by dilated capillaries.

FIG. 2. A section of the kidney to show fairly normal glomerulus and artery.

FIG. 3. Section of the kidney to show the necrosis of the tubules.

PLATE 29, FIG. 4. Artery in the medulla, to show normal thickness of wall and normal perivascular space.

FIG. 5. A typically healthy nerve cell from the hypoglossal nucleus.

FIG. 6. Two nerve cells from the hypoglossal nucleus, showing normal amount of Nissl substance.

FIG. 7. An average nerve cell in the dorsal sensory portion of the vagus nucleus, showing the almost complete absence of Nissl substance.

FIG. 8. Two nerve cells from the dorsal vagus nucleus, showing that the only Nissl substance is that forming a peripheral ring.

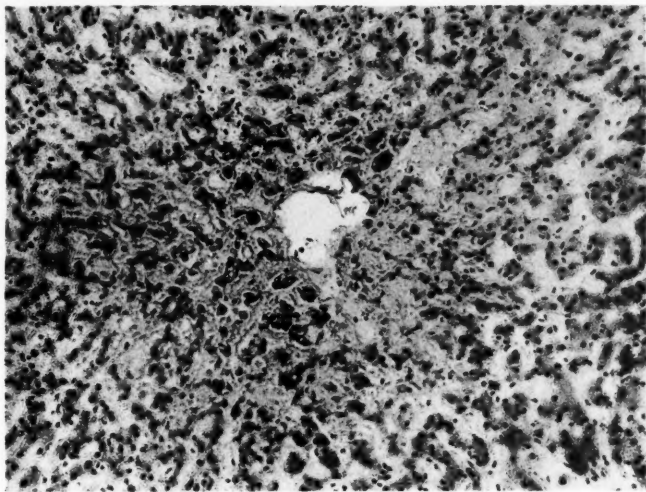


FIG. 1

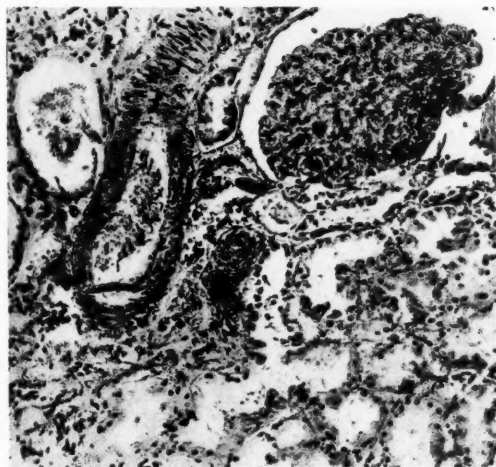


FIG. 2

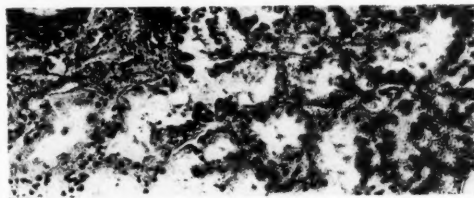


FIG. 3



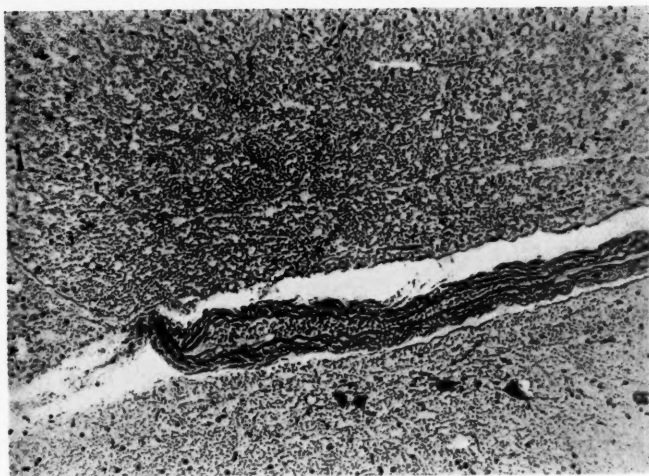


FIG. 4

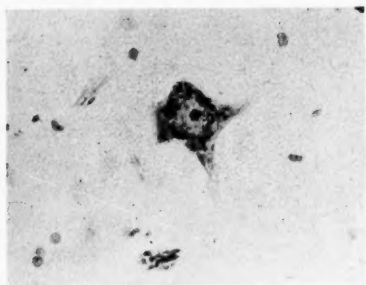


FIG. 5

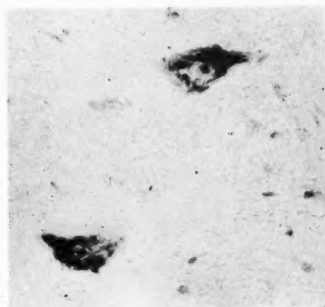


FIG. 6



FIG. 7



FIG. 8





# THE IMPORTANCE OF FUNCTIONAL ACTIVITY IN THE AETIOLOGY OF NERVOUS DISEASES

By W. JOHNSON

(From the Neurological Department, Guy's Hospital)

With Plate 30

## *Introduction.*

THE value of rest in the treatment of disease is now fully recognized, being first firmly established by John Hilton in his classical lectures on Rest and Pain.

A critical consideration of his teaching leads directly to the recognition of another principle which is equally important. The fact that activity is injurious to a diseased part raises the question: 'What influence may severe functional activity have on structures which—although not grossly diseased—are still affected to such an extent that the exercise of even ordinary function taxes them to the utmost?' Under such conditions, can a sudden period of activity, or the strain of a laborious occupation, determine the onset and the character of the symptoms which a patient presents? Further, is it possible that such symptoms would never have occurred but for the activities to which the individual has exposed himself?

As a result of his study of nervous diseases Edinger has long since expressed his belief that symptoms are, in large part, exhaustion phenomena, and that they are closely associated with the nature of the patient's activities.

Up to the present his theory (1), and the evidence he brings forward in support of it, do not appear to have received adequate attention. A discussion on the aetiology of nervous diseases usually gives the greatest prominence to 'selective action' of poisons, and then attention is turned to hereditary instability of the nervous system, trauma, mental stress and strain, chill, and lowered resistance. As recently as the last International Congress of Medicine, in the discussion on parasyphilis, the exhaustion theory was given scant consideration.

*The Theory of the Selective Action of Toxins.* In a general way this theory does appear to afford explanations of the commoner diseases of the nervous system. The toxin of tabes dorsalis, for example, destroys the sensory neurones in the posterior columns of the spinal cord. That of general paralysis of the insane causes degeneration in those cerebral neurones which are concerned with

the exercise of the intellectual functions. Other poisons—alcohol, lead, arsenic, and those present in diphtheria and diabetes—act chiefly on peripheral nerves. It has been urged that possibly there exists a definite chemical difference between nerve cells and nerve fibres—and even between groups of either—which accounts for the manner in which one poison selects one part of the nervous system and another an entirely different part.

But a brief application of this theory in detail at once exposes its inadequacy. *Tabes dorsalis* will serve to illustrate this. As has been mentioned above, the characteristic condition in this disease is a destruction of the sensory neurones in the posterior columns. The toxin, it is said, either has a selective action for these neurones, or else, owing to the arrangement of the blood-supply, excess of it reaches the posterior columns. These explanations leave us completely in the dark on several important points. First, that in the majority of cases the lumbar region of the cord is chiefly affected and the patients present symptoms of leg tabes. Secondly, one side may be more severely affected than the other, so that clinically the knee and tendo-Achillis jerks may be lost only in one leg. Thirdly, in other cases the cervical region of the cord shows the greatest degree of change and clinically we are presented with arm tabes. Finally, when we turn to the eye symptoms of this disease, we are forced to the conclusion that the same toxin, which in the spinal cord selected the sensory system, has in the brain picked out part of the motor system, namely, the third nerve; and that this is so despite the fact that the other cranial nerves, whether motor or sensory, are but rarely affected.

On this theory, also, it is difficult to explain the variation in the mode of onset which individual cases present. In some the onset is extremely rapid, while in others it is slow and progressive. Then again, the occurrences of severe relapses in one case and periods of marked improvement in another are equally unsatisfactorily explained.

It is possibly on account of the number of variables which come into consideration in any discussion of the toxin theory that this latter holds its ground so well. The abnormal types, it is said, are the result of a change in the relation of the variables. Thus, the nature of the toxin, the amount and frequency of the dose, together with the state of the patient's powers of resistance, must all be taken into account. In any given case it is quite impossible to estimate the relative value of any of these factors, and consequently it is futile to meet (or to advance) statements which may be based on them.

Therefore it becomes necessary to explore the whole question more fully, with a view to providing a more adequate interpretation of the conditions encountered. Where we have the same toxin 'selecting' different parts in different patients, it is justifiable to assume that an additional factor, and probably a more important one than selection, is at work.

*The Exhaustion Theory.* In the consideration of this theory, the first question to be decided is what is the effect of excessive activity on relatively normal structures. This has been answered by numerous observers. Hodge

first drew attention to the differences in the nerve cells in bees before and after flight. Gustav Mann's classical experiment on dogs has also shown that exhaustion changes occur in the visual cortex of one eye, which had been exposed to a bright light, and not in that of the other, which had been kept blindfolded.

More recently Edinger and Helburg (1) have shown by experiments on rats:

(1) That slight changes occur in the spinal cord in normal rats, which by various contrivances are compelled to perform excessive muscular activity with both fore and hind limbs.

(2) That, if in any way the rat is abnormal, e. g. rendered anaemic or is chronically poisoned, these changes occur much more rapidly and to a much greater degree.

The changes they describe consist in a degeneration mainly affecting the posterior columns of the spinal cord, and chiefly in the lumbar and cervical regions (corresponding to the position of the leg and arm fibres). Slight changes were also present in the lateral columns.

Histologically, the appearance presented was a degeneration and breaking up of the medullary sheaths, as shown by staining with osmic acid, with, later, complete disappearance of the sheath and secondary changes in the axis cylinder. In addition, the anterior horn cells showed the sequence of changes characteristic of exhaustion, viz. swelling of the nerve cell, eccentric position of the nucleus, and finally breaking up and disappearance of Nissl's granules.

The close similarity which these appearances present to those which are described as the result of chronic poisoning at once attract attention. The importance of this experimental evidence cannot be over-estimated. If exhaustion alone is able to cause the typical degenerative changes, which are usually ascribed to toxic action, the urgency of investigating the relation of functional activity to symptoms clinically becomes at once apparent.

The object of this paper is to do this, by presenting an analysis of some nervous diseases in the light of Edinger's exhaustion hypothesis. The cases which will be cited are taken from those attending the Neurological Out-patient Department at Guy's Hospital under the care of Dr. Hertz. In addition are included five cases of primary optic atrophy from ophthalmological out-patients under the care of Mr. Eason.

Each case has been investigated individually, and care has been taken, as far as possible, to avoid leading questions. In several instances, the onset of symptoms was so remote that inquiry into the nature of the trouble first noticed, or the movements of the patient just prior to the onset, proved valueless. In the majority of cases, though, a clear history could be obtained of both. Under these circumstances, then, we are dealing with an aetiological factor which can be examined carefully and of which therefore the full significance can be practically judged—a condition of affairs which cannot be applied in the consideration of the toxin theory.

*Fatigue in the normal individual.* The clinical effects of fatigue will be first

shortly considered. After long and severe races it has been remarked that heaviness and feelings of deadness result in the lower limbs, together with definite weakness of muscles. Marked ataxia in the legs has also been observed, and in addition aching pains and tenderness in the muscles.

As the result of observation on the runners in a certain harriers' club I have found that exaggeration of the knee- and tendo-Achillis jerks, together with the tendency to ankle clonus, is extremely frequent. For example, after a cross-country race of  $7\frac{1}{2}$  miles I found that out of a team of 14 runners, 12 had exaggerated, while the remaining 2 had diminished tendon reflexes. Knapp and Thomas (4), examining 48 runners after a Marathon race of 24 miles, found the knee-jerks diminished in a much larger proportion of cases. This is probably accounted for by the excessively trying condition of the competition. After one day's rest normal jerks were present in all cases.

In some similar observations on soldiers, in one case where a history of syphilis was obtained, the lost jerk never returned, and the onset of tabes was determined (quoted by Edinger).

An interesting group is formed by the occupation neuroses and atrophies. These are well-defined clinical conditions which are directly traceable to various forms of occupation. Taking into consideration the number of people engaged in special employments, the relative frequency of neuroses is not great. This is because the normal person, provided he is given adequate periods of rest—and fatigue is the signal which warns him that rest is essential—is capable of training his muscles up to any state of perfection. Constant practice under these conditions enables the individual to develop a 'physiological capacity' far beyond the normal.

If, however, the individual's powers of resistance are lowered by such factors as alcoholism, influenza, neurasthenia, insomnia, insufficient food, then fatigue will become established earlier and symptoms result. Amongst our cases it seems possible to distinguish two types; the commoner one—an ataxy—due to a loss of the co-ordinating power which is necessary for the performance of the particular movement. This is accompanied by a condition of disordered sensation (paraesthesia) in the part used. Writers and pianists form examples of this group.

The other type, which is rarer, may be found singly or complicating the first group, and is characterized by muscle atrophy. It occurs in those occupations where a certain muscle is required to be continually in a state of contraction—as for example the opponens pollicis in watchmakers, who hold a pair of fine forceps in their hand. As other examples I may mention two men who worked in a leather factory for thirty-five and fifty years respectively. They presented weakness and atrophy of the left arm and hand, which, it appeared, was constantly in use for lifting and supporting the frame on which the leather were stretched.

*Discussion and Examples.*

The first condition of chronic toxæmia to be considered is parasyphilis. Until recently parasyphilis was regarded as being caused by a vague toxin which was closely associated with syphilis. But inasmuch as no typical specific lesions could be demonstrated pathologically—if vascular changes be excepted—it was impossible to classify it as a purely syphilitic condition.

The work of Noguchi in demonstrating the spirochaete pallida in the cerebral cortex of general paralytics and in the spinal cord of cases of tabes dorsalis has revolutionized the whole attitude as regards parasyphilis. Further, the successful production<sup>1</sup> of definite specific lesions in rabbits by inoculating them with the cerebral cortex of cases of general paralysis of the insane conclusively shows that parasyphilis as such does not exist. It is a condition dependent on the presence of the spirochaete pallida, and so is a true syphilitic disease. Realizing this, Head (2) has stated that he regards tabes as a parenchymatous myelitis and general paralysis as a parenchymatous encephalitis which occur as the result of proliferation of nerve elements and neuroglia, induced by the presence of the specific organism.

Possibly a still more exact interpretation of tabes and general paralysis is obtained when we consider these new data in the light of the exhaustion theory. The presence of the spirochaete pallida in the central nervous system is tangible evidence that the syphilitic toxin is being there manufactured. The fact that the cerebrospinal fluid gives a positive Wassermann reaction leads us to conclude that the whole nervous system is bathed in these toxins. This must lead to a general lowering of vitality of all the nervous tissues; in other words, it leads to a condition of chronic poisoning of the central nervous system. Under these circumstances degenerative changes occur in those portions of the nervous element on which the greatest amount of stress falls. Thus tabes is to be regarded as the result of the exhaustion of the neuro-muscular mechanism and general paralysis of the higher cerebral neurones.

The findings of morbid histology fall into line with this view. There exists primary degeneration and death of the neurones, followed by secondary changes in the neuroglia which are possibly entirely proliferative and compensatory in nature.

Further support of this view is furnished by the fact that very similar pathological changes to those seen in tabes dorsalis are produced by totally different toxins. Marked degeneration in the posterior columns of the spinal cord have been described in certain cases of lead poisoning, ergot poisoning, and pellagra.

<sup>1</sup> Previous failures in this experiment are explained by the fact that a sufficiently long time was not waited for the lesions to develop. At least three times as long is necessary (about 120 days) as after inoculations with typical secondary or tertiary material—which indicates that in general paralysis of the insane we are dealing with an attenuated virus.



	Type.	Number.	Percentage of Total.
Leg	. . . . .	21	60
Eye	. . . . .	10	27
Arm	. . . . .	3	8
Sphincter	. . . . .	2	5

*Analysis of Cases.* 1. *Tabes dorsalis.* The commonest type of this disease is a marked degree of leg tabes associated with slight eye tabes. In the thirty-six cases of this condition which I have investigated no less than twenty-one (rather less than 60 per cent.) came up complaining of leg symptoms. In eleven of these (about 30 per cent.) the patients followed a definitely laborious occupation. They consisted of dock labourers (two), engineer's labourers (two), general labourers (two), carmen (two), market porter (one), slaughterer (one), and lastly a railway guard who had heavy luggage to deal with. All of them were on their feet the whole day, lifting and carrying heavy articles for nine or ten hours a day. One man, the slaughterer, habitually worked longer hours. His symptoms came on very rapidly—pain in the hips and legs, followed by reeling when walking. On questioning him it was ascertained that he had just previously been working sixteen to eighteen hours a day. His work consisted mainly of carrying heavy portions of meat. Another man, a carman, walked into London with a load of vegetables and back again in the evening—a total distance of thirty miles. He did this often twice a week. Originally he had been a policeman.

The remaining ten cases (making up the 60 per cent. which presented leg symptoms) consisted of patients whose occupation, without being excessively laborious, still necessitated much walking or standing. Two of them, a water board inspector and a commission agent, spent their whole day in house to house visits. In several cases I have noticed that stair-climbing especially has an injurious effect. Another was a clerk who, although he sat to his occupation during the day, walked six miles daily to his office and, in addition, would take an extra walk of ten miles often twice a week. A fourth was a cabinet-maker, who worked standing at his bench ten hours a day. He was an enthusiastic cyclist. One was a bus-driver with marked ataxia, and at first his symptoms would appear to defy explanation. Investigation, however, revealed that although he had driven a bus for several years he had previously been a bus-conductor for nine years. Also that, as a driver, the position in the driving seat throws most of the body-weight on the legs, and the incessant use of the foot-break calls for constant movement on the part of the legs. It is noteworthy that he had experienced no trouble whatsoever in the arms from holding the reins. In a cab-driver no adequate history of the onset of his leg symptoms was obtained. Another man, a baker, worked long hours, had heavy sacks of flour to move about, and was kept standing all day.

The last three cases in this group were women—forming 8 per cent. of the whole series. In two instances the patients followed active employment. One was a domestic servant, but gave no history of exceptionally hard conditions of labour. The other, however, was employed long hours at a factory, and, in order



to save expense, she would often walk to and from work. The journey used to take her more than two hours each way.

The third case proved to be of great interest. It was that of a woman in whom the symptoms in the legs directly followed a difficult confinement. The patient was in labour continuously for forty-eight hours, and the child had eventually to be removed with instruments and was still-born. The pains in the legs came on within a few days, and ataxia was marked as soon as the patient began to get about again.

Some explanation of the leg symptoms in tabes is afforded by an attempt to analyse the mechanism involved in the ordinary act of walking. The all-importance of the sensory side, as compared to the motor side, of the nervous system becomes apparent. Co-ordination and not muscular exertion is the predominating factor. To establish this co-ordination, impulses from muscle sense, bone sense, joint sense, and tactile impression from the soles of the feet are essential. These sensory impressions are given no rest even during sleep. Sufficient muscle co-ordination and tone are preserved, by means of which the still sleeper is easily distinguishable from the one in whom life has become extinct.

It is conceivable, therefore, that in a 'potential tabetic', where the central nervous system is chronically poisoned, those sensory neurones conveying the muscle, joint, and bone sense which are so essential for co-ordinated movement will eventually become the seat of exhaustion and present degenerative changes. In the same way lightning pains and crises are to be regarded as evidence of disorder of the sensory system.

Although all the cases quoted above showed typical Argyll-Robertson pupils, the eye symptoms were of secondary importance and had been ignored by the patient. The loss of the reaction of the pupils to light was also present in the remaining fifteen cases now to be considered. The exhaustion theory offers an intelligible explanation for the occurrence of Argyll-Robertson pupils, as a short consideration of the question is sufficient to establish the fact that the light reflex is one of the most—if not the most—active reflexes in the body. From the moment when the eyes open in the morning to the moment when they close again at night, the pupils are constantly adapting themselves to variations occurring in the light. The accommodation reflex, which is preserved in tabes for some time after the light reflex has disappeared, is in comparison a less active one.

The next commonest eye symptom is ptosis, and following that strabismus. This association of Argyll-Robertson pupil, ptosis, and strabismus has led to the dictum that tabes selects the third cranial nerve. If we inquire into the function of the third nerve it is seen that activity furnishes an equally good solution of the symptoms. The constant activity of the light reflex has already been touched on. The third nerve supplies the majority of muscles which are concerned with the activity of the eye. It innervates the levator palpebrae superioris, whose duty it is to keep the eye open. (In passing it may be noted that one of the earliest signs of the fatigued state is a drooping of the eyelids.) With the

exception of the superior oblique and the external rectus, all the external ocular muscles draw their nerve supply from the third nerve. If, therefore, selection is all-important, the commonest form of strabismus should be one resulting from a paralysis of the third nerve muscles. This is not borne out clinically. The commonest strabismus in tabes is that due to paralysis of the external rectus—a muscle supplied by an entirely different nerve, the sixth. This same muscle is affected in another toxic paralysis—diphtheria. Why this should occur does not seem clear, unless it be assumed that it is an exceptionally important muscle in the mechanics of the eye. One case in my series suggests that possibly the presence of some error of refraction serves to throw an extra strain on one ocular muscle or group of muscles. This was a man who seven years previously had attended the Royal Eye Hospital, Moorfields. Mr. Flemming, who has been good enough to look up his notes of the case, writes to say that the patient was ordered glasses for defective vision in the right eye. When we saw him the symptoms in this right eye were marked. The pupil was small and did not react to light. There was complete ptosis, and in his case a paralysis of the internal rectus. In the left eye the pupil reacted sluggishly to light and there was a slight degree of ptosis.

As far as the cranial nerves are concerned, therefore, it seems fair to state that those which are functionally most active are chiefly affected in this disease. Compared to them the others are but rarely involved.

In ten cases (27 per cent.) the eye trouble had first drawn the attention of the patient to his condition. In four the symptoms had been vague, and consisted of indistinct vision, headache, and eye-strain. One of these was the man with the error of refraction who has been mentioned above. Another was a clerk who had followed the same occupation all his life. A third was a wharf-foreman, whose work was chiefly writing out orders and checkings for goods—which was practically clerking. The fourth was a leather-dresser, but any influence this employment could have on the eyes seemed difficult to trace. In the three last of these cases the legs were normal when first examined. In one of them the tendo-Achillis jerk disappeared on one side during the time he was under observation.

The remaining six of the group (16 per cent.) were found to have primary optic atrophy when first seen. Inquiry into their form of employment resulted in an interesting observation which it is hard to regard as a pure coincidence. They were, with the exception of one man, all found to be working in artificial light. The first was a gas stoker, whose duty it was to feed the gas furnaces. He stated that the glare from the fire was so intense that unless the eyes were shaded the effect was 'blinding'. He had followed the same employment for nineteen years. The second was an electrician who worked in dark places by the light of an electric lamp which was always close to his eyes. He often used to see bright red balls in the eyes on turning away from the light. Another was a coal-porter who worked most of the time in cellars by candlelight. After coming into the daylight he usually could see very little for the first quarter of an hour, and he

stated his horse would appear to be a different colour. A fourth worked as a shop-assistant for twenty-three years in a room poorly lit by gaslight, which was necessary in the daytime as well as at night. The fifth had worked underground as a coal-miner for nineteen years. Finally, the last case had been a bricklayer, and no history similar to that obtained in the other cases was given.

The effect which glare and artificial light may have on the eyes was discussed at the International Congress of Medicine (5) of last year. It was there stated that ordinary daylight had little or no deleterious action on normal or even diseased eyes, but that glare from any source—as, for example, the reflection of bright sunlight from snow or sea—would produce blindness. Edinger cites the case of one of his patients where the eye symptoms of tabes came on directly after such an experience. It was further stated at the Congress that the ultra-violet rays, which are present so largely in artificial light (especially from powerful arc lamps), exert a specially injurious effect upon the eyes. It seems probable, therefore, that such a factor, acting on an optic nerve which is already under the influence of a chronic poison, produces optic atrophy.

The phenomena giving rise to Benedict's law may here be briefly considered. This states that a patient with marked symptoms of tabes in the legs usually has slight eye symptoms and vice versa. That this should be so is further support for the exhaustion theory. A laborious occupation in which there is little eye-strain produces a condition of leg tabes. On the other hand, a sedentary occupation with much eye-strain would tend to produce eye tabes. Further, it is interesting to note that in cases of primary optic atrophy, after blindness is complete, the leg symptoms tend to improve. As a result of his blindness, the patient is compelled to lead a quiet, sedentary existence, in so far as muscle activity is concerned. In not one of our cases of primary optic atrophy was ataxia a marked symptom.

Arm symptoms were first noticed only in three cases (8 per cent.), and, contrary to general experience, these were all men. Two were very typical examples of amyotrophic tabes in whom the atrophy had occurred in the small muscles of the hand, chiefly in the thenar and hypothenar eminences. They were both labouring men of the type called 'navvies'. Their work consisted mainly in using a pickaxe and swinging a heavy sledge-hammer, necessitating the exercise of much muscle power.

The third case was a tailor who came for subjective sensory disturbances in the right hand, which prevented him from using the needle and scissors at his work. There was practically no loss of motor power in the hand—the trouble appeared to be mainly due to a disturbance of co-ordination. This man presented an interesting eye condition. There was ptosis of the right eye, together with weakness in closing the left eye. The right pupil was larger than the left and did not react to light. The left pupil reacted sluggishly to light. The explanation of his symptoms appeared to be as follows. He lived by the sea and took a great interest in shipping, and during the day was continually using a telescope which was applied to the right eye. The left eye was kept

shut. The average number of times he would use the telescope in a single day never fell below thirty.

In the consideration of exhaustion phenomena, therefore, it seems necessary to distinguish two types. One, the exhaustion of the sensory side which occurs in the over-use of the fine co-ordinated movements—such as we assume has occurred in leg tabes and in the arm of the tailor. The other, the exhaustion of the motor side in those cases where powerful muscular work has to be done, as in the first of the two cases of arm tabes. Of this nature, perhaps, is the atrophy of leg muscles which occurs in the later stages of tabes. The tabetic, as is well known, stamps his feet firmly on the ground when walking, in order to augment the few afferent sensations which still remain to him. By so doing excessive use is made of the leg muscles.

In only two cases (5 per cent.) were troubles with micturition first noticed. In both these patients, however, as physical signs of tabes in legs and eyes were well advanced, the urinary symptoms must be regarded as a late development. Edinger, however, records one case where bladder trouble developed as a result of the patient being obliged to hold his water for the greater part of a whole day.

Hertz has shown<sup>2</sup> that the trouble with micturition owes its origin to a diminished loss of sensibility in the bladder. As a result of this the patient allows the bladder to become repeatedly over-distended. Eventually the vesical musculature gives out before this strain and incontinence results.

As a result of questioning several of our cases one is led to believe that impotence also is an exhaustion phenomenon.

2. *General paralysis of the insane.* This disease is characterized by degeneration and destruction of those cerebral neurones which are concerned with the exercise of the intellectual functions. It is common in towns and amongst civilized nations, and appears to be a direct result of the hurry and bustle of business life and of the demands which it makes on the mental powers. The comparative freedom of Eastern nations from the condition would appear to be due to the more quiet vegetative existence which they lead. In confirmation of this is the observation that general paralysis has increased to a remarkable extent in Japan since the recent recrudescence of national activity.

This condition of mental exhaustion and decay forms a close analogy to the view which has been presented of tabes. In the latter the exhaustion is of the neuro-muscular mechanism, and in the former of the mechanism concerned with mental power. The analogy may be pushed closer. In general paralysis we are presented with primary optic atrophy and the same pupil changes that obtain in tabes. Further, clinically, we recognize a condition—*tabo-paresis*—in which a picture of tabes is presented together with the mental change found in general paralysis. The inference from this can only be that, given the external conditions of life necessary to produce both diseases, the patient with the suitable

<sup>2</sup> It is possible to pour rapidly a relatively large quantity of fluid into the bladder of tabetics without causing any desire for micturition.

soil, viz: a central nervous system under the influence of the syphilitic toxin, will develop a combination of the symptoms of the two disorders.

The other manifestations of general paralysis of the insane, such as fits, hemiplegia, which at first do not appear to fit in with a theory of exhaustion, are to be explained by the gross syphilitic lesions which occur in the vessels of the brain in this disease.

I have reported (6) nine cases of a certain form of mental deficiency in children which is analogous to general paralysis. In it no symptoms arise until the child is sent to school and large demands are made on its mental powers. Definite mental weakness then appears and is progressive as long as educative attempts are continued. The Wassermann test is found to be positive. The explanation of these cases is of the same nature that we are considering here. There is a basis of poisoning of the nervous system which, in the presence of activity, leads to a degenerative process in those neurones which are the subject of the activity.

3. *Other chronic toxæmias.* If all toxins showed no tendency to damage one particular portion of the nervous system more than another, and if the amount and degree of toxæmia were the same in every case, then it might fairly be expected that the same form of activity would produce the same clinical picture, no matter what the particular toxin present might be.

Despite the wide variation in the toxic power of the different toxins, clinical conditions closely simulating tabes are produced by totally different toxic substances. The first to be considered will be alcohol.

*Chronic alcoholism.* The nervous disorder in this condition is most commonly confined to the legs. The condition may be so markedly ataxic as to simulate very closely tabes, and is then known as peripheral pseudo-tabes. This term Déjerine has applied to any form of peripheral neuritis in which ataxia is the outstanding feature. One of our cases was a very good example of this type. He was a market porter by occupation, and came up complaining of severe pains in the legs and unsteadiness in walking, which was very extreme. The knee-jerks and tendo-Achillis jerks were absent on both sides. The pupils were almost pin-point, but were equal and reacted to light, and the Wassermann reaction in the blood was negative. The diagnosis was alcoholic neuritis—pseudo-tabetic variety. Twelve months later the man's symptoms had quite disappeared and the knee-jerks and tendo-Achillis jerks had returned.

One example each of the other forms of alcoholic neuritis will serve the purpose of this article.

*Leg type.* A dock labourer, whose work consisted in pushing a truck containing bags of sugar weighing from 2 to 6 cwt., presented himself with pains and weakness in the legs. There was marked weakness in the anterior tibial group of muscles, resulting in a condition of dropped foot on both sides. The tendo-Achillis jerk was absent on both sides and also the knee-jerk on the right side.

*Arm type.* A coachman presented symptoms in his right arm—his driving



arm. They consisted in neuralgic pain down the upper arm, a feeling of numbness and deadness in the fingers, so that he had difficulty in holding the reins. There was also definite weakness in grip and slight loss of power in the extensors of the forearm.

*Combined type.* A man—a horse-clipper by trade—exhibited symptoms in arms and legs. These symptoms came on after a rush of work, during one of the 'seasons' for horse-clipping. The work necessitated his standing, stooping, and kneeling all day long, and both arms were required for using the machine. When seen he was hardly able to walk, and there was marked condition of dropped foot on both sides. The hand grips were weak and both wrists were dropped—the forearm extensors being almost completely paralysed. Six months later recovery was almost complete.

Korsakow's syndrome would appear to occupy the same position with regard to alcoholic peripheral neuritis and alcoholic dementia as does tabo-paresis to tabes and general paralysis of the insane. In this syndrome the patient exhibits the typical condition of peripheral neuritis affecting the legs, together with the form of mental change, i. e. loss of memory for recent events, which is so closely associated with alcoholism.

At the present moment authorities still differ as to whether the Argyll-Robertson pupil can be produced by chronic alcoholism. The opinion of the majority doubtless is to regard it as definite evidence of syphilitic infection. Others, however, are convinced that it can occur solely as the result of alcoholic poisoning. Oppenheim, in his text-book of neurology, supports this view.

In chronic alcoholism, in cases where the nervous system is not put to any particular strain, as in those individuals who lead a luxurious existence, no symptoms of nervous disorder arise. It is then rather the cardio-vascular and digestive systems which are attacked, producing diseases which are well recognized—cirrhosis of the liver, myocarditis, and renal disease.

A detailed analysis of a series of cases of alcoholic neuritis is in course of preparation.

*Chronic plumbism.* In the same way, cases of lead poisoning are seen in which there is little or no nervous disorder. Clinically their symptoms consist of severe anaemia, abdominal colic, albuminuria, and general lassitude. A blue line may often be seen on the gums.

In fact, very few workers in a lead factory develop leg symptoms or even the typical wrist-drop as compared with those who exhibit the condition of general poisoning. An investigation into the nature of the employment supplies a reason for this.

There were six cases with undoubted lead poisoning who attended for weakness in the wrists—more commonly the right was worse than the left. Apart from blurring of vision and retinal changes there were no eye troubles. The legs were affected in one case only. This was a man whose work consisted in lifting and carrying sheets of iron. This he did by using a long pair of tongs, with which he used to dip the sheets into molten lead. He described it as heavy



work. Both wrists were dropped. The tendo-Achillis jerks were absent on both sides and the knee-jerks much diminished. Eighteen months after giving up his work the wrists had become normal, the knee-jerks brisk, but the tendo-Achillis jerks were still absent.

The next case did exactly the same kind of work. His legs, however, were normal, except for vague pains. He dipped four or five hundred tanks daily into the molten lead. The first thing he noticed was inability to hold the tongs firmly. When examined there was wrist-drop only on the right side, and the flexor longus pollicis especially showed marked paresis.

A third man was employed in using a long rod of iron at the end of which was a skimmer. His duty was to skim off the crust from the surface of the molten lead. In this way the left wrist was chiefly affected. He stated that the weight of the rod was supported chiefly by the left hand.

The fourth patient was engaged in using a shovel for the purpose of feeding a lead furnace. He had marked wrist-drop on both sides.

In all these forms of occupation the strain thrown on the wrist is very great. A short personal trial will be sufficient for the amateur to prove this to his own satisfaction.

The fifth case was a painter. This man was a left-handed individual, and the left wrist was most severely affected. He used a heavy brush, the handle of which was held as shown in the photograph (Pl. 30). The thumb holds the handle pressed against the palm of the hand. As a result there was marked weakness of the long flexors of the thumb, somewhat similar to the condition in the man mentioned above. Recently he had also been on 'ceiling work', in which he worked with the arm held above the head. The deltoid on the left side showed definite paresis.

The last case was that of a married woman who did housework. The origin of the plumbism was never cleared up. Her doctor wrote to say she had had no medicine containing arsenic or any other metal from him, but that two or three months previously he had treated her for severe menorrhagia. It is possible, therefore, that the patient had procured abortion by means of one of the popular remedies containing lead.

Numerous noteworthy cases are described by Legge and Goadby in their book *Lead Poisoning and Lead Absorption*, where also a list of references to the literature may be seen.

Taking the most classical example of selective action of poisons—that of lead and the musculo-spiral nerve—the exhaustion theory brings several interesting points into observation. 'Dropped wrist' is chiefly found in compositors, painters, and in those whose occupation largely consists in wrist work. It has been calculated that a painter, in the course of his work, accomplishes something like 3,000 extensions of his wrist every hour. Add to this the fact that he uses a heavy brush over a sticky surface, and it is possible to estimate the amount of work demanded of his muscles. The way in which the extensors are always affected in peripheral neuritis also lends support to the exhaustion theory, as

physiological experiments show that extensor muscles are more easily fatigued than the flexors.

It becomes, therefore, of the utmost importance to analyse the various cases individually. In this way Edinger has demonstrated that in the two different types of house-painters, i.e. oil and distemper painters, different forms of paralysis result. In the oil painter, who uses a small brush held in his fingers, after the fashion of a pen, the paralysis is quite different from the one which occurs in distemper painters, where the man uses a heavy brush, the handle of which is grasped by the whole hand. In the same way the omission of the supinator longus from the paralysis is explained by the fact that the movement of this muscle is not associated with these forms of occupation.

Rarer forms of nervous disorders in chronic lead poisoning again approximate to certain alcoholic sequelae. Peripheral neuritis of the legs may simulate alcoholism and tabes. A chronic form of mental change indistinguishable from general paralysis of the insane also occurs. And, finally, there is a condition of muscle atrophy which occurs as the result of lead poisoning.

4. *Diabetic and diphtheritic neuritis.* As yet I have insufficient cases of either of these two conditions to be of any value.

The principles of the exhaustion theory have been further applied to: (1) familial diseases of the nervous system; (2) primary spastic paraplegia, progressive muscular atrophy, and its allied conditions, amyotrophic lateral sclerosis and bulbar paralysis. The reader will find this discussed in Edinger's latest publication.

It would seem possible also to include the muscular dystrophies and the conditions classed as focal diseases under the same view.

In the former there is a congenital inability of the muscles to perform ordinary functions, and the attempt to use them leads to atrophy. This occurs chiefly in the muscles concerned in the gross movements of the trunks and limbs, which are especially active in children, who form the majority of patients with this class of disorder. The pseudo-hypertrophic type may be regarded as a compensatory phenomenon, for at first a true hypertrophy of muscle is present, secondary changes appearing later.

In focal diseases it is suggested that the chemical change which results in activity is sufficient to produce a local trauma which determines the site of the lesion. In anterior poliomyelitis, for instance, the virus affects most commonly the lumbar region of the cord, i.e. that portion concerned with the activities of the legs. Where the arms have been affected it has been possible to trace a connexion between the paralysis and the activity which has preceded the onset.

#### *Summary of Conclusions.*

(1) That a poison which circulates through the body, though it may show some particular selective action for various parts, does not cause sufficient damage of itself to produce symptoms. That these symptoms only occur through

the agency of another factor—functional activity—and that, failing the presence of this additional factor, the patient may never develop any definite disease, although his general power of activity may be considerably lessened. Thus but a small percentage of patients with syphilis develop symptoms of tabes and general paralysis. Further, when these do develop they do not appear, as a rule, until several years (ten or more) after the primary infection. This is in marked contrast to true cerebro-spinal syphilis, which tends to occur in as many months. The same wide difference is shown in the results of treatment of the two conditions. Antisyphilitic treatment in tabes and general paralysis causes little, if any, improvement.

(2) That inquiry into individual cases shows there is a close association between a patient's symptoms and the nature of his activities; and that the various poisons, although widely different in nature, do tend to produce clinical conditions which nearly approach each other. As examples, the toxins of syphilis, alcohol, and lead have been quoted as producing respectively (a) tabes, tabo-paresis, and general paralysis; (b) alcoholic neuritis, Korsakow's syndrome, and alcoholic dementia; (c) lead neuritis, dementia, and a combination of both conditions. Further, both alcohol and lead produce weakness of the extensors of the forearm (so-called selection of the musculo-spiral nerve) while sparing the supinator longus. Often other muscles supplied by the median and ulnar nerves are affected, and it is accordingly quite impossible to explain them by selection—different muscles being affected in different patients.

(3) The nervous system, therefore, in these forms of chronic toxæmias is to be regarded as subnormal, owing to the presence of the poison. The individual is indeed a potential patient, who, if put under any sufficiently exacting conditions, will inevitably develop symptoms in the part exhausted. On this view the multiplicity of symptoms which occur in such conditions as tabes or alcoholism becomes more intelligible.

(4) That it seems possible that a patient's mode of life and particular form of activity may be just as important in the determination of his symptoms as, in the Darwinian theory, similar conditions are in the production of 'special characters'.

#### *Treatment.*

The influence which this should have on treatment is apparent. In nervous diseases, more than any other condition, prophylaxis holds out the most promising outlook, as the presence of symptoms in a patient is actual evidence of a destruction of nervous structures which is practically irreparable.

Realizing this, the early diagnosis of (a) hereditary subnormal conditions, (b) tabes dorsalis, or (c) any of the forms of toxic neuritis becomes extremely important, in order that the patient may be removed from such conditions, which, if persisted in, would inevitably produce symptoms.

In addition, the question is opened up of originating new lines of treatment, based on the recognition of the evil results which functional activity in a sub-normal structure will produce.

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Discussions on and the literature of Edinger's *Aufbrauchtheorie* will be found in the *Neurologisches Centralblatt*, 1905, 7, 8, and 11.

## DESCRIPTION OF PLATE.

PLATE 30. To show the manner of holding a heavy brush by painters.



Illustrating the method of holding the brush in the fifth case of lead poisoning.





## BLOOD-PRESSURE ESTIMATIONS IN DISEASE BY THE OSCILLATORY AND AUDITORY METHODS

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(From the Physiological Laboratory, University of Aberdeen)

With Plates 31-34.

THE clinical part of this investigation was carried out in the wards of the Aberdeen Royal Infirmary, on fifty-one patients presenting, for the most part, pathological conditions of circulation. The principle involved was the correlation of blood-pressure estimations by (*a*) the auditory method, (*b*) the tactile method, and (*c*) the graphic method of the Erlanger sphygmomanometer. In practice, the method adopted was to raise the pressure within the armlet well above that required to obliterate the radial pulse; then to lower the pressure in stages generally of 10 mm. (method of interrupted escapement); and to register a tracing at each level. During this process attention was directed to the determination of (*a*) the first appearance of a sound (auditory systolic index), (*b*) the first appearance of a pulse at the wrist (tactile systolic index), (*c*) alterations in the character of the auditory phenomena, and particularly of that which gives the index of diastolic pressure. The auditory diastolic reading was verified by lowering the armlet pressure to zero, so as to avoid congestion in the limb, and then raising the pressure sufficiently to elicit the diastolic indication.

### *Method.*

The usual precautions in blood-pressure estimation were observed—the armlet (12 cm. broad) at heart level, absence of muscular contraction in the limb under examination, &c. One of us attended to the manipulation of the Erlanger apparatus, whilst the other was responsible for the determination of the pressures required. An Oliver (1) tambour (phonendoscope), accurately but not tightly strapped over the site of the brachial artery at the bend of the elbow, was employed for the investigation of the auditory phenomena. In almost every case the auditory systolic index was found to be at least as high as the tactile, generally, in fact, a few millimetres higher. Such a relation is to be regarded as essential. In any case in which there was obtained a higher reading by the tactile method, we regarded the auditory method as defective, unless by some alteration, e.g. in the arrangement of the tambour, it was found

possible to establish the proper relationship. The actual pressures were read on the mercury manometer of the Erlanger instrument.

*Indices of Systolic and Diastolic Pressure.*

In reading the systolic pressure by means of the tracing, we have adopted the Recklinghausen-Erlanger (2, 3) index—the pressure at which there is to be seen a sudden increase in the amplitude and a separation of the limbs of the oscillations. As we have elsewhere pointed out, this index is often unsatisfactory, being unreadable or giving readings at variance with those yielded by the auditory and tactile methods (see records of Nos. 1, 6, 11, 12, 13, &c.). The chief importance of the oscillatory method, however, is in relation to the estimation of diastolic pressure.

In our table of results we have included two estimates of diastolic pressure interpreted from the oscillation record: (1) diastolic pressure as estimated by the index of Erlanger (Column 'E.D.'), and (2) diastolic pressure estimated by the index adopted by us (Column 'O.D.'). The index utilized by Erlanger is that of the lowest pressure at which the oscillation is maximal. On the other hand, there is evidence to show that the diastolic pressure corresponds with a pressure lower than one which is associated with maximal oscillations (4). On grounds which we have stated elsewhere (5) we prefer, as the diastolic index, the average of the armlet pressures just before and just after a sudden and marked decline in the oscillations from the maximal or approximately maximal size. It is apparent that if the external pressure be lowered by 10 mm. stages, the sudden diminution in the oscillation at any particular stage might have been associated with any of the preceding 9 mm. Since we prefer the slower method of interrupted escapement (as being more efficient than that of continuous escapement), we consider it safer on the whole to take the average, though we do not regard it as an exact indication in any particular case. In Pl. 31, Fig. 1, for example, in which the average of 70 and 60 has been taken, giving 65 as the diastolic pressure estimated by the oscillation method, it is probable that the actual point lies not at the mean, but nearer 60, thus bringing the auditory and oscillation estimates into agreement.

We have adopted the term 'approximately maximal' for the sake of convenience, to indicate a phase at which the oscillation, though appreciably smaller than maximal, is still large and separated by no abrupt or extensive diminution from it. Such an approximate maximum is often followed by a sudden and extensive diminution. We regard the latter as the diastolic indication in such a case. Sometimes, on the other hand, the oscillation declines very gradually through two or three phases before any abrupt lessening occurs, and in some instances there is no sudden and extensive change at any phase. Under such conditions the interpretation of the tracing presents serious difficulty, and different readings may be made from the same tracing by different observers.

It is generally agreed that the auditory systolic index coincides with the first of the five phases described by Ettinger (5). These phases are—(1) sharp, clear sound; (2) muffled or murmurish; (3) loud and clear; (4) dull; (5) abolition of sound.

With regard to the index of diastolic pressure there has been much difference of opinion. The two distinct points which have been suggested and utilized are (1) the beginning of the fourth phase, and (2) the fifth phase. In a study of a series of normal adults, we have shown that the acceptance of the fifth phase, or lower limit of sound, as the diastolic index, would lead to erroneous results in the estimate of diastolic pressure. On quite separate grounds, already stated (4, 7), we consider the true index of diastolic pressure to be the point at which the sound becomes suddenly diminished in intensity and duller in character—that is to say, we read diastolic pressure at the beginning of the fourth phase. In the study of the normal series above referred to, we established the fact that the fourth phase was very variable in extent and in many cases exceeded to a great extent the estimates most generally accepted. In very few of the present series investigated amid the distractions of hospital wards, did we find a protracted fourth stage; in fact, in an outstanding majority its duration extended to a few millimetres only, so that the point of abolition of the sound was nearly the same as that of the sudden change which constitutes the diastolic index.

#### *Results.*

As compared with the series of observations on normal adults there was much greater variation in the character of the Erlanger tracings and much greater difficulty in many cases in making a diastolic reading. This is easily intelligible in view of the varied abnormal conditions of the vascular system in the cases examined, and the altered conditions of the arteries, influencing the changes, in (*a*) transverse diameter and in (*b*) length, at each pulse-beat which are concerned in producing the volume oscillations.

There was frequent and serious discordance between the oscillatory and the auditory indications; in such cases the oscillation index was as a rule higher by varying amounts (Fig. 2). In 30 cases selected as showing decided discrepancy, the range of such discrepancy is from 10 mm. to 40 mm. with an average of 19.8 mm. Taking the Erlanger oscillation index, the range and the average of discrepancy are greater, being respectively 15 mm. to 50 mm., and 31.03 mm. Such discrepancies as 13, 15 mm., &c., have been found even when the change from the approximate and not the actual maximal has been taken (Fig. 3; Pl. 32, Fig. 4). The auditory index may agree with the change from the actual maximum (Fig. 5), with a change from the approximate maximal (Pl. 33, Fig. 6), or with a point at a later stage in the tracing. This later stage may be prominent as showing a marked diminution in the amplitude of the oscillation at that point (Fig. 7), or may be quite inconspicuous, so that the auditory index is unrepresented by any very definite or outstanding feature in the tracing (Pl. 34, Fig. 8).

TABLE I.

The following abbreviations are used in this table: O.S. = Systolic index by oscillation method (Recklinghausen-Erlanger index). A.S. = Systolic index by auditory method. T.S. = Systolic index by tactile method. O.D. = Diastolic index by oscillation method using the index we employ. A.D. = Diastolic index by auditory method. E.D. = Diastolic index by oscillation method using index as employed by Erlanger. P.R. = Pulse rate.

No.	Age.	Sex.	Nature of case.	P.R.	O.S.	A.S.	O.D.	A.D.	E.D.	Remarks.
1	34	m.	Ant. crural neuralgia	75	180	125	85	60	90	Marked discrepancy (25 mm.) bet. O.S. and A.S. O.D. much above A.D. if first decline from max. taken; below, if phase of most marked dim. of oscill. magnitude taken. Defective adjustment of tambour, &c., might make A.S. too low, but on the other hand such would make A.D. too high.
2	68	m.	Morbus cordis	66	120	130	85	78	90	O.S. and A.S. not much different; T.S. = 124; relation of T.S. to A.S. normal; O.D. = 85 dim. from max.; A.D. = 78. Next phase in tracing shows greater dim. This would make O.D. = 75, agreeing with A.D., but would involve the taking of a dim. from an oscillation much less than max.
3	12	m.	Paroxysmal haematuria	84	105	110	65	60	90	O.S. doubtful—possible agreement with A.S.; O.D. and A.D. not much different.
4	55	m.	Chronic nephritis	84	?	155	105	100	110	Readings nearly agree both as regards S. and D.
5	74	f.	Senile	78	?	190	115	110	140	O.S. unreadable. A.D. coincides with first marked diminution from 'approx.' not from absol. max. 'Approx.' is much less than absol. max.
6	61	m.	Arterio-sclerosis (cerebral)	(1) 84	230	272	155	126	170	(1) O.D. is 29 mm. above A.D.—taking first phase of marked decline from max. as index.
			"	(2) 88	200	217	155	150	160	(2) See Pl. 32, Fig. 5. There was an interval of 3 weeks between (1) and (2). O.D. remains pretty constant, while O.S., A.S., and A.D. are changed.
7	34	m.	Gastric haemorrhage	74	170	172	105	91	110	T.S. = 164. O.D. = change from actual max.; A.D. agrees with next change—the most extensive in the tracing.
8	22	m.	Chronic nephritis	84	180	174	105	96	120	Virtual agreement as regards syst. O.D. difficult to read.
9	81	m.	Senile	56	?	248	125	85	130	O.S. doubtful; wide discrepancy between O.D. and A.D. Evidence has been adduced elsewhere that the first readings of A.S. and T.S. (which are in practical agreement) greatly overestimate the actual syst. pr. on account of the state of the arterial tube (see 'Heart', 1913, iv. 312). Pulse-pressure not really great. <sup>1</sup>
10	63	m.	Senile	72	2160	162	95	90	110	O.S. equivocal—large oscillations before A.S.
11	47	m.	Chronic syphilitic cirrhosis	78	110	90	65	59	70	See Pl. 31, Fig. 1.
12	66	m.	Carcinoma coli	84	140	120	95	82	110	O.S. decidedly higher (20 mm.) than A.S.; O.D. change from approx. maximal. Last maximal = 110, last approx. maximal = 100.

<sup>1</sup> The max. oscillation in this case almost corresponded with the actual systolic pressure, the obliteration reading (248 mm.) being, as already described, an extreme exaggeration of the actual pressure. This recalls a case in which C. J. Martin, using a mercury manometer to record the oscillation, found the maximum oscillation to be near the systolic pressure.

TABLE I (continued).

No.	Age.	Sex.	Nature of case.	P.R.	O.S.	A.S.	O.D.	A.D.	E.D.	Remarks (continued).
13	21	m.	Acute nephritis	90	?	122	65	86	80	T.S. 120; O.S. doubtful; O.D. somewhat indefinite; A.D. does not correspond to any striking change in oscillations. See Pl. 32, Fig. 4. O.S. and A.S. in agreement. T.S. = 170 in normal relation to A.S.; O.S. doubtful; O.D. after approx. max. nearly agrees with A.D.
14	62	m.	Chronic intoxication	82	170	170	105	92	130	O.S. difficult to fix, no indication corresponding with A.S.; O.D. (change from actual max.) higher by 12 mm. than A.D.
15	30	f.	Gastric	90	180	180	105	94	110	Syst. and diast. virtual agreement by all methods. O.S., T.S., and A.S. agree; O.D. = change from approx. max. O.S. and O.D. about 10 mm. above A.S. and A.D. O.S. lower than A.S.; O.D. and A.D. nearly agree. O.S. doubtful; pretty large oscillns. before A.S.; O.D. 13 mm. higher than A.D.
16	24	f.	Cardiac; mitral and aortic stenosis	100	?	140	77	65	80	O.S. probably agrees with A.S.; O.D. after approx. max. 15 mm. above A.D.
17	1	m.	Diabetes	72	120	126	55	54	60	O.S. and O.D. unreadable.
18	55	m.	Dilated stomach	69	190	192	115	100	120	O.S., T.S., and A.S. agree; O.D. = 105. Change from approx. max. This is also most marked change. A.D. = 90.
19	78	f.	Senile	84	190	180	95	80	100	O.S. slightly above A.S.; O.D. uncertain.
20	30	m.	Chronic nephritis	68	120	130	74	70	85	O.S. corresponds with no recognizable change in tracing; O.D. taken as change from approx. max.
21	30	m.	Left basal pleurisy	80	?	130	75	62	110	O.D. taken as change from approx. max.; O.D. practically agrees with A.D.
22	37	f.	Mitral stenosis	90	140	140	95	80	100	O.S. lower than A.S.; O.D. after approx. max. 25 mm. above A.D. O.S. 10 mm. higher than A.S. A.D. disagrees with both first fall from actual max. and more marked diminution coming later, being lower than the former and higher than the latter. T.S. = 152.
23	22	m.	Aortic stenosis (slight)	51	?	120	?	50	90	O.S. higher than A.S.; A.S. confirmed by T.S., which is only very slightly (2 mm.) lower; O.D. and A.D. correspond; T.S. = 100.
24	43	m.	Aneurysm (asc. aorta)—Right	90	200	200	105	90	110	O.S. and O.D. unrecognizable = gradation in oscillation throughout.
			" Left	90	190	190	105	80	110	O.S. in agreement with A.S.; large oscillation before O.S. O.D. (change from actual max.) is 15 mm. above A.D. Nearly agree if next phase taken.
25	20	m.	Morbus cordis	108	125	121	255	90	130	See Pl. 34, Fig. 8. O.S. agrees with A.S. or is 10 mm. lower according as tracing is interpreted.
26	54	f.	Chronic bronchitis	108	180	190	115	90	140	O.S. and A.S. agree; O.D. 105 by change from max. Larger change from 100 to 90. A.D. = 72 does not correspond with any recognizable feature in the tracing. O.D. and A.D. would differ still more if last phase of max. oscillation taken.
27	40	m.	Hypostatic pneumonia; nephritis	68	130	130	75	72	90	
28	68	m.	Emphysema and cardiac pain	68	210	220	125	100	130	
29	19	m.	Acute nephritis	81	180	170	115	98	120	
30	47	f.	Gastric	69	110	102	65	64	70	
31	35	f.	Neurasthenia. ? Addison (1)	72	?	120	?	60	85	
32	38	m.	" (2)	82	?	109	?	58	95	
			Alcoholic neuritis and incipient delirium tremens	96	150	150	115	100	120	
33	62	m.	Cardiac and chronic nephritis	75	220	230	135	110	140	
34	28	m.	Ch. bronchitis and emphysema	102	150	150	105	72	110	

TABLE I (continued).

No.	Age.	Sex.	Nature of case.	P.R.	O.S.	A.S.	O.D.	A.D.	E.D.	Remarks (continued).
35	30	f.	Albuminuric retinitis	111	2150	160	125	115	130	O.S. difficult to read. O.D. taken after actual max. is somewhat above A.D. after next phase agrees with A.D.
36	46	m.	Arterio-sclerosis	84	190	160	105	90	110	O.S. much (30 mm.) above A.S. See Pl. 31, Fig. 3.
37	57	f.	Facial spasm	66	150	150	85	80	110	See Pl. 33, Fig. 6.
38	69	m.	Senile	82	180	194	205	70	110	O.S. decidedly below A.S., though there are large oscillations earlier. O.D. is higher than A.D. by anything up to 25 mm. according to phase taken as index.
39	49	f.	Polycythaemia	102	210	210	115	95	130	Difficult to interpret tracing. A.D. corresponds with no indication in tracing.
40	57	m.	Chronic nephritis	87	230	229	145	122	150	O.S. agrees with A.S., while T.S. (220 mm.) is 9 mm. lower. O.D. is 23 mm. higher than A.D., taking change from actual max.
41	62	m.	Arterio-sclerosis	66	190	200	115	87	130	O.S. is 10 mm. below A.S. O.D. is much too high (28 mm.) by phase following approx. max.
42	21	m.	Pneumonia (convalescent)	84	110	110	75	54	80	O.S. and A.S. agree. O.D. (change from max.) is higher than A.D. by 21 mm.
43	46	f.	Nephritis; arterio-sclerosis	120	220	258	165	149	170	O.S. much lower (38 mm.) than A.S., while O.D. is higher (16 mm.) taking the marked diminution from the max.
44	57	m.	Nephritis; arterio-sclerosis	72	190	191	115	82	120	See Pl. 33, Fig. 7. O.S. and A.S. agree. O.D. higher (33 mm.) than A.D. by phase after actual max.
45	81	m.	Senile	63	210	214	115	110	130	Virtual agreement of O.S. and A.S., and of O.D. and A.D.
46	35	m.	Aneurysm of aorta—Left	78	?	130	77.5	78	80	Left arm:—O.S. impossible to fix. O.D. pretty nearly agrees with A.D. taking first phase of decline from actual max.
			" " Right	78	?	122	67.5	62	80	Right arm:—O.S. doubtful; large oscillations, gradually increasing. O.D.—taking most marked change in the gradual decline from the max.—agrees pretty well with A.D., but this change comes well on in the process of decline far from the max. Conditions were complicated by presence of aortic aneurysm.
47	66	m.	Ch. bronchitis and emphysema	75	150	122	95	78	100	See Pl. 31, Fig. 2. O.S. is 28 mm. above A.S. Latter is confirmed by T.S. (122 mm.)
48	49	m.	Chronic nephritis	78	?	116	77	75	90	O.S. impossible to fix. O.D. by change from approx. max. practically agrees with A.D. Change from actual max. makes O.D. 10 mm. higher.
49	38	f.	Ch. nephritis; pleural effusion	93	?	98	?	72	90	Very small oscillations; O.S. and O.D. unreadable.
50	40	m.	Aneurysm—asc. and trans. aorta	100	140	140	75	60	80	O.S. and A.S. agree. O.D., taking change from approx. max., is higher by 15 mm. than A.D.
51	22	f.	Morbus cordis	92	?	110	75	75	90	Tracing difficult to interpret for systolic index.



Averages of diastolic pressures or of pulse-pressure obtained in such a heterogeneous collection of cases are of no intrinsic value except as a means of comparing the results of the methods employed. It is of interest, however, to note the *range* of diastolic pressure. In these 51 cases it varies (1) from 150 to 50 mm. estimated by the auditory method, (2) from (a) 165 to 55 mm. estimated by the oscillation method, using the index we have adopted, (b) 170 to 60 mm. by the oscillation method, using the Erlanger index. This is a very much more extensive range of variation than was found in the series of normal adults, where the diastolic readings were from 82 to 50 mm., the average being 65.7 mm. by the auditory method.

The pulse-pressure taken by the auditory method varies from 163 to 26 mm. Taking the pulse-pressure as the range between the oscillation systolic index and (a) the oscillation diastolic index as we have read it, and (b) the oscillation diastolic index as read by Erlanger, we find the extent of such range to be (a) 95 to 25 mm., and (b) 90 to 20 mm. In the normal series, previously referred to, the range was 73 to 22 mm., with an average of 46 mm.

Taking the whole series, the range of variation, as regards diastolic readings and pulse-pressures, is found to be only slightly different when gauged by the oscillatory and by the auditory methods respectively. Though this is true as regards the extreme limits of the pressures in the series, the discordance between the results of the two methods is, in many cases, as stated above and shown in the tabular statement and in the tracings, a very serious one.

The discordance in the present series of pathological cases between the oscillatory and the auditory estimations of diastolic pressure and of pulse-pressure range is in contrast to that obtaining in our series of normal young adults, where there was practical agreement—the average values of diastolic pressure being 68 mm. by the oscillatory method (using our index), and 65.7 mm. by the auditory method. In the mixed collection of pathological cases the averages work out as under: Diastolic pressure (a) by auditory method, 84.6 mm.; (b) by oscillation method, (1) using the index we employ, 99.0 mm., (2) using Erlanger index, 109 mm. Pulse-pressure (1) by auditory method, 75.1 mm.; (2) by oscillation method, using Recklinghausen-Erlanger index for systolic pressure and (a) our index for diastolic pressure, 65.2 mm., or (b) Erlanger index for diastolic pressure, 55.7 mm.

In the presence of such discordance we prefer the auditory readings, in view of the evidence available as to the complexity and variability of the oscillation method in different conditions, and the reliability of the auditory indications as verified by comparison with direct measurement of the internal pressures, by valved manometers, in an experimental schema and in animals; in both of these the auditory index was found to be a remarkably accurate guide to the actual diastolic pressure (4, 7).

We desire to express our thanks to Professor MacWilliam for valued advice, and to the members of the staff of the Aberdeen Royal Infirmary for permission to examine the cases in their wards.

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## DESCRIPTION OF FIGURES.

PLATE 31, FIG. 1. Oscillation diastolic = 65, change from maximal. Auditory diastolic = 59.

FIG. 2. Gradual declension. Oscillation diastolic = 95 = first decline from actual maximum. Auditory diastolic = 78. Oscillation systolic = 150—much higher than aud. syst. and tact. syst.

FIG. 3. Oscillation diastolic = 105, change from approximate maximum. More extensive change from 100 to 90 would make oscill. diast. = 95. Aud. diast. = 90.

PLATE 32, FIG. 4. Oscillation diastolic = 105, by diminution from approx. max., which is third phase from actual max. By next and more extensive dim. = 95 in practical agreement with aud. diast. = 92. This latter is a change from a phase that cannot be called even approximately maximal.

FIG. 5. Oscillation diastolic = 155. Change from maximal practically agrees with aud. diast. = 150.

PLATE 33, FIG. 6. Oscillation diastolic = 85, change from approx. max., which is already much less than actual max., there being a gradual dim. from 110 (actual max.) to 100 and from 100 to 90. Aud. diast. = 80.

FIG. 7. Oscillation diastolic = 115, change from maximal. Aud. diast. = 82 corresponds with more sudden dim. at fourth phase after last maximal phase, the intermediate phases showing gradual declension.

PLATE 34, FIG. 8. Oscillation diastolic = 135, change from approx. max.; no more extensive step later. Aud. diast. = 110—corresponds with nothing definite in tracing.

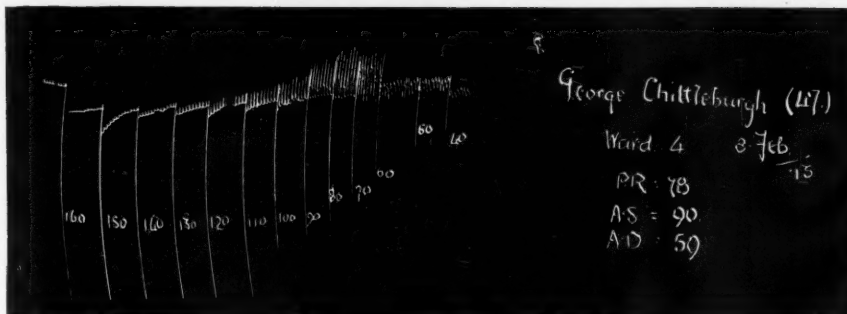


FIG. 1

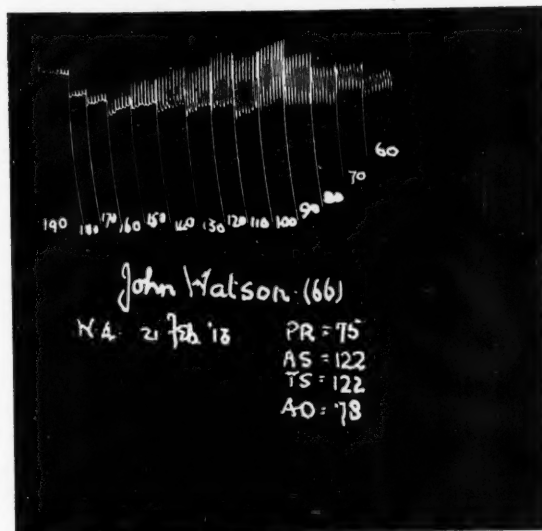


FIG. 2

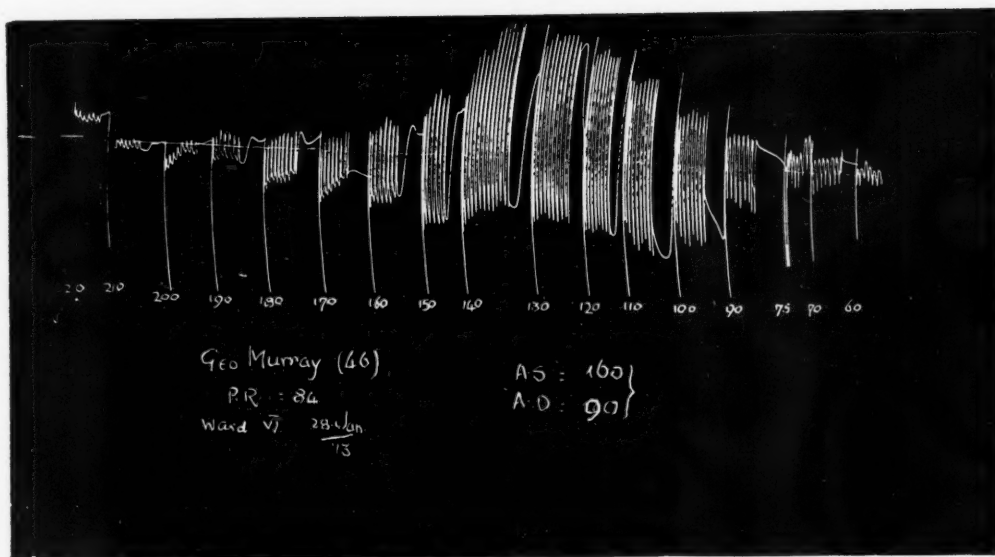


FIG. 3



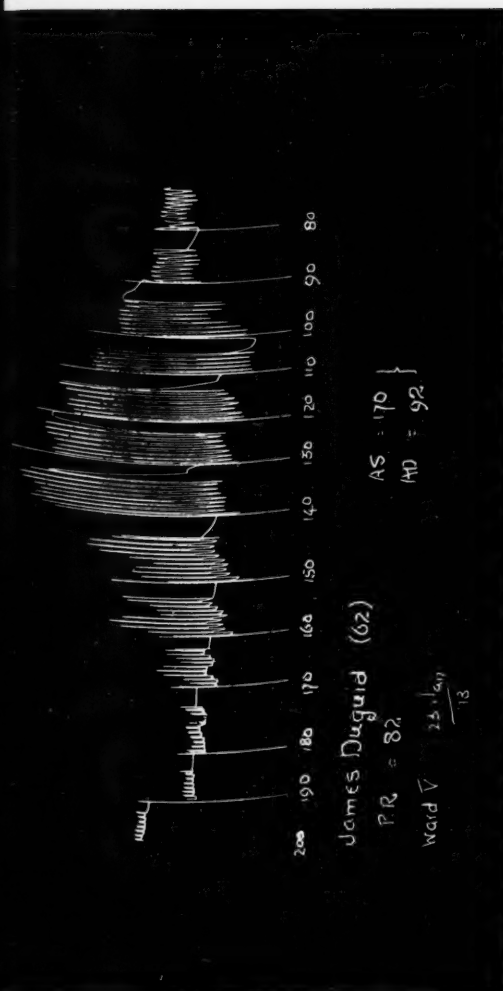


FIG. 4

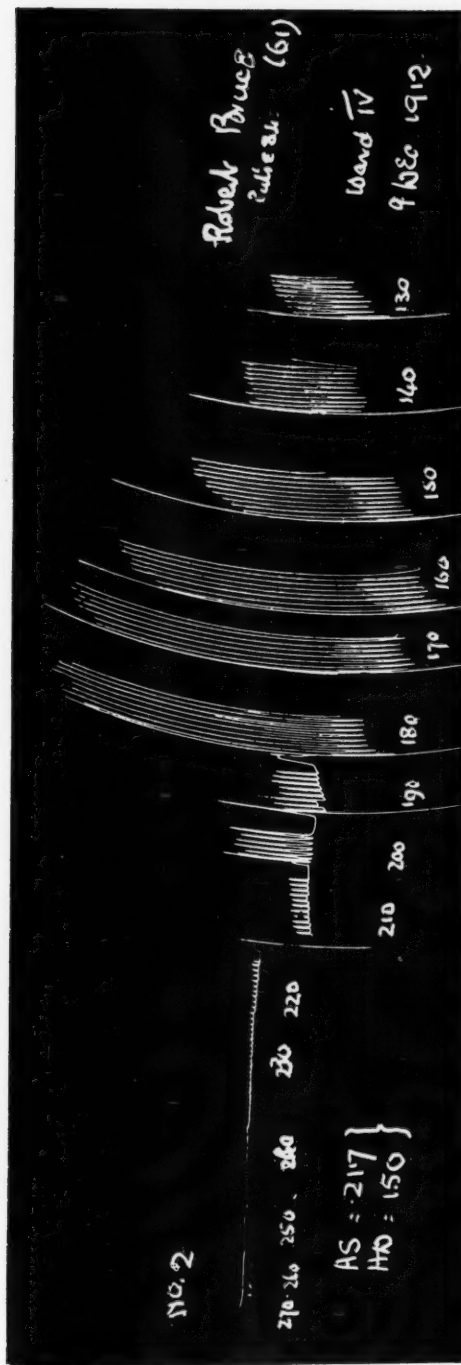


FIG. 5





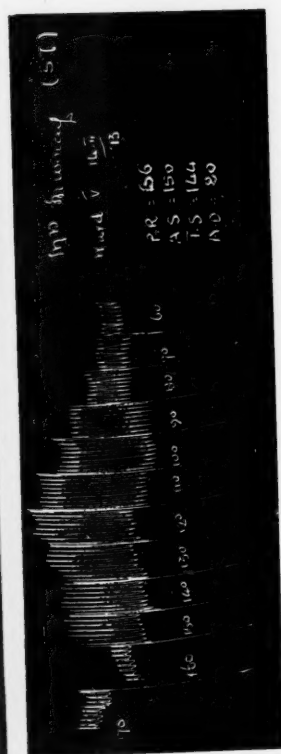


FIG. 6

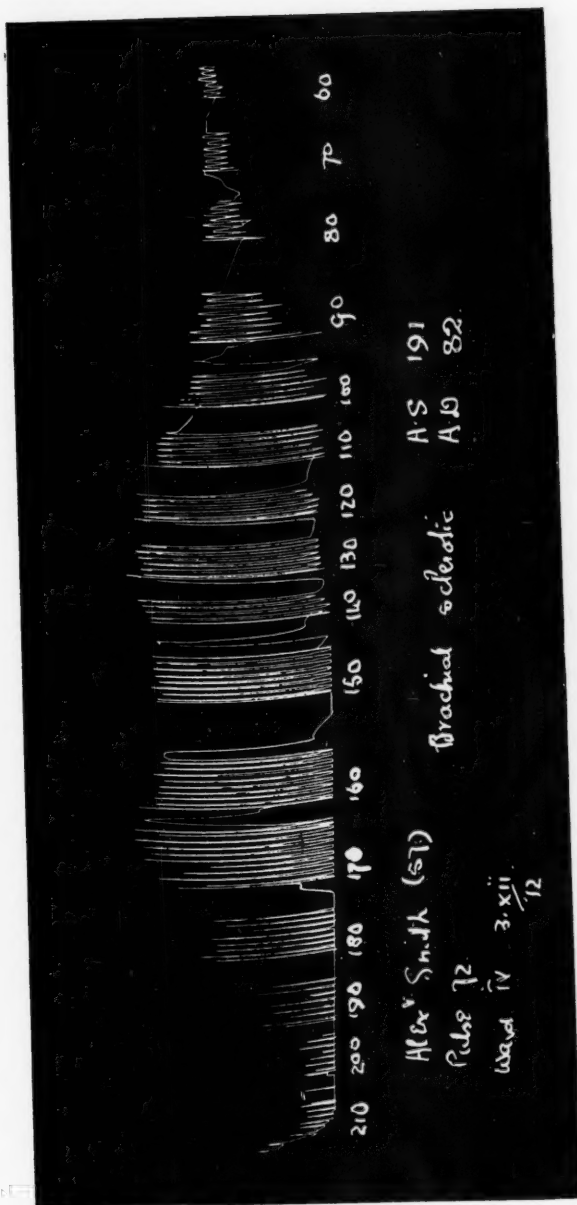


FIG. 7



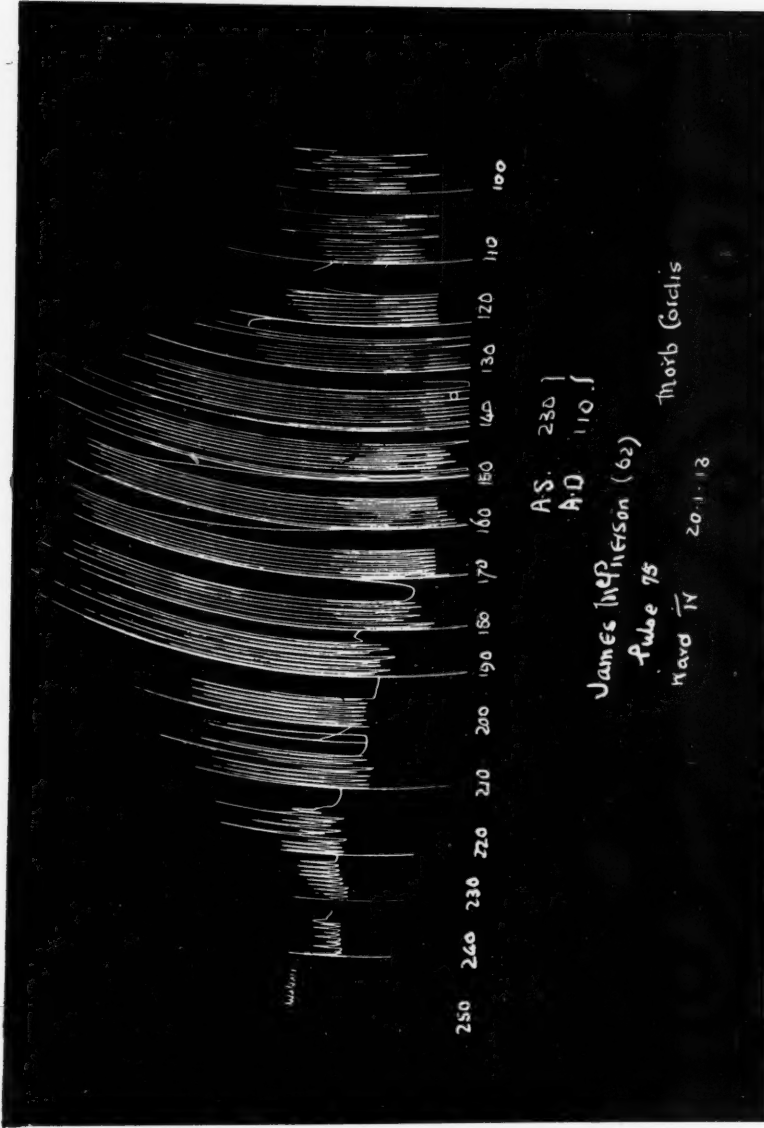


Fig. 8



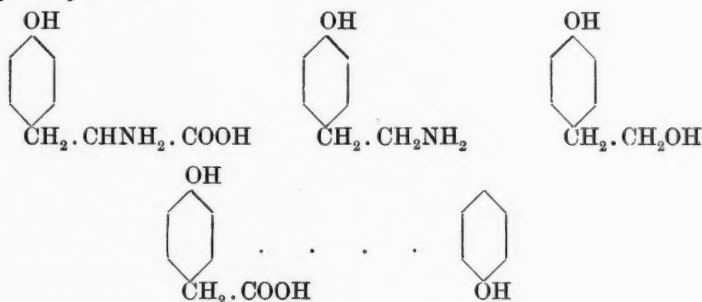
# THE FORMATION OF $\beta$ -IMINAZOLYLETHYLAMINE IN THE ILEUM OF CERTAIN CONSTIPATED SUBJECTS. WITH A NOTE ON THE URINE IN CONSTIPATION

By N. MUTCH<sup>1</sup>

(From the Laboratories, Guy's Hospital)

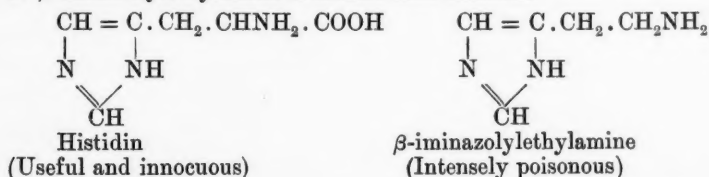
THE changes which may be induced in the lower products of proteolysis by intestinal bacteria are remarkable in that the toxicity of the resulting compounds varies very greatly. Probably in many cases highly poisonous substances are first formed by simple alterations in the structure of the useful nitrogenous products of enzyme action, and are changed subsequently into simpler innocuous but useless products by further bacterial action.

E. g. 1. Tyrosin :



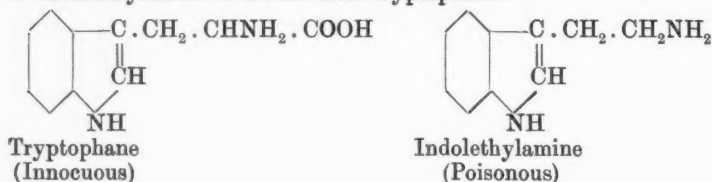
In this series useful tyrosin is first changed to highly poisonous hydroxyphenylethylamine and ultimately becomes relatively innocuous phenol. In normal intestines most of the tyrosin is absorbed unchanged, whilst the residue passes rapidly into the colon and is destroyed.

2.  $\beta$ -iminazolyethylamine is formed from histidin.



<sup>1</sup> Working in tenure of the Beane Research Studentship in Pharmacology and aided by a grant from the British Medical Association.

## 3. Indolethylamine is formed from tryptophane :



It would appear probable that in the colon, where bacteria are present in billions and the work of destruction can be taken up by relay after relay of organisms, relatively innocuous end-products arise. The highly toxic intermediate bodies are to be sought for where selected bacteria not too numerous and not too versatile in their chemical potentialities come into contact with the products of proteolysis. In the present paper it is shown that the lower end of the ileum of constipated subjects offers such suitable conditions, and that its flora is one that can form  $\beta$ -iminazolyethylamine (which will be referred to hereafter as  $\beta$ -iminazo) from histidin in those patients who present one of the symptoms of chronic  $\beta$ -iminazo poisoning, namely a subnormal blood-pressure.

*The Conditions in the Ileum.*

Radiographic observations have proved that food passes rapidly through the small intestine and reaches the ileocaecal valve about three and a half hours after leaving the stomach. It then passes into the caecum at a slower rate, so that altogether about four hours are occupied by the passage from pylorus to colon. The chyme in the lower end of the ileum is fluid, and consists of products of digestion, bile pigments, stercobilin, and ferments dissolved in an almost neutral isotonic solution of sodium chloride and sodium carbonate. Experimental fistulae in dogs show that 6 per cent. of absorbable food reaches the caecum. This is composed entirely of the simplest products of digestion, including tyrosin, histidin, arginin, lysin, leucin, alanin, and aspartic acid. Observations of the effluent from fistulae of the lower part of the ileum in man show that after a test meal about 14 per cent. of the protein can be recovered in the form of simple products of proteolysis : also that when an ordinary mixed diet is given the reaction of the chyme is faintly acid, the acidity corresponding to about 0.1 per cent. of acetic acid and being due to organic acids presumably formed by bacterial action on carbohydrates. The bacteriology of the small intestine is still in its infancy. Eyre has, however, shown that in normal subjects after death, the lower end of the ileum may contain several varieties of aerobic bacteria, but only in small numbers. He has kindly made a personal communication to me of the following facts. He examined the contents of the lowest parts of the ilea of subjects dead from accidents, or brought into hospital dead, or who had died with some mental disorder. During the short interval between death and the autopsy the bodies were kept in a cold chamber. The



contents were frequently sterile, but on various occasions a few colonies of the following bacteria were grown: *B. coli*, *B. proteus*, and *Streptococcus*. In these researches anaerobic bacteria were not investigated. From these considerations it would appear that slight modification might render the terminal coils of the ileum most suitable for the production of poisonous amines; and indeed the modifications often found in association with chronic constipation are just such as would encourage these bacterial reactions. Bismuth traverses the small intestine just as quickly in constipated patients as in normal individuals, but the normal delay in the terminal coil of the ileum may be greatly increased, and the lowest portions of the ileum become distended with chyme, which collects in abnormally large quantities and remains under the influence of the restricted flora of that region for an unusually long period before being passed into the bacterial destructor, the colon. These conditions alone would favour the production of intermediate bodies, but the process is further encouraged by an increase in the richness of the flora of the ileum which has been brought to light by Eyre's researches. He examined the bacteria removed at operation by small swabs from the lowest coil of the ilea of sixteen constipated patients. In only one instance did he fail to cultivate pathogenic organisms. Even in this case the ileum may have been infected, only a very small portion of its contents being removed by the swab. The growth was far more luxuriant than that obtained from the normal ilea already referred to. In this research also anaerobic bacteria were not considered. The author has carefully examined on fifteen occasions the colon and lower portions of the ileum removed by Sir Arbuthnot Lane at operation and has noted the following points. Although the whole abdomen of constipated patients emits a faecal odour, great differences can be observed between the offensiveness of the various portions of the intestinal canal, and the ileocaecal valve forms a great dividing line. If the lumen of the ileum is opened up by a longitudinal incision and its contents exposed as far as a point 3 or 4 mm. from the caecal aspect of the ileocaecal valve the odour emitted is extremely faint, but immediately after the valve has been cut through completely the usual nauseating vapours of faecal matter become urgently obvious. It is quite evident that the contents of the caecum do not usually regurgitate through the ileocaecal valve. This was demonstrated more completely still by bacteriological methods. Immediately after the abdominal wall had been opened at operation a ligature was tied round the ileocaecal junction. Swabs were subsequently taken from the caecum and lowest portion of the ileum. From the former most luxuriant cultures were obtained; from the latter comparatively slight growth. On two occasions a large portion of ileum, about 75 cm. in length, was removed and cultures made from its contents at various points with similar results in the two cases. One is quoted below.



faeces cultures of *B. coli* capable of changing histidin to  $\beta$ -iminazo, whilst numerous other strains of *B. coli* obtained from the same source were without such power. This may be a question of environment, and it is conceivable that *B. coli* of any kind can be educated to act on histidin by repeated cultivation in histidin media, but the proposition lacks experimental proof at present. The fact that from one sample of faeces only relatively few colonies of histidin-splitting *B. coli* can be obtained and many more colonies of *B. coli* which are useless for this conversion, suggests that the question is not merely one of education of the bacillus by its environment.

*The Action of  $\beta$ -iminazo.*

$\beta$ -iminazo is a very potent drug; it is not destroyed by the liver, and a specific organism has already been isolated which is capable of producing it from histidin. It causes a great fall in blood-pressure in cats, dogs, and monkeys. All its actions vary from species to species but produce symptoms resembling those of anaphylactic shock. By analogy it became probable that a depressor effect would be produced in man also. The following results warrant that conclusion:

*Case A.* A well-nourished healthy girl, aged 23, lying in a supine position after operation for femoral hernia, and taking a mixed maintenance diet. Compound infusion of gentian was given for several days and observations made on the blood-pressure. The readings on the first day were rejected to avoid error from excitement caused from the unusual procedure. On the subsequent days observations were repeated until a constant value was obtained for each arm. In this way disturbance due to any slight excitement occasioned by the visit was controlled. Regular hours were selected for making the observations, 10 a.m. and 2.30 p.m., in order that diurnal variations might not interfere with the accurate interpretation of the readings. Similar precautions were taken throughout the experiments described in this paper.

Day.	B. P. 10 a.m. mm. of Hg.	B. P. 2.30 p.m. mm. of Hg.	Difference.	Mean.
1	110	112	+ 2	- 1
2	113	109	- 4	
3	107	107	0	
*4	101	90	-11	-11
*5	107	96	-11	

\* On these days 0.004 grm. of  $\beta$ -iminazo was added to the compound infusion of gentian at 10 a.m. and at 1.30 p.m. The subject was unaware of the addition.

*Case B.* A woman of 32 years lying in bed three weeks after the removal of her colon. The wound had completely healed and there had not been any pyrexia. The diet was a normal mixed one.

Day.	B. P. 10 a.m. mm. of Hg.	B. P. 2.30 p.m. mm. of Hg.	Difference.	Mean.
1	108	106	- 2	-1.5
2	101	100	- 1	
*3	102	90	-12	-12

\* On this day 0.006 grm. of  $\beta$ -iminazo was added to the compound infusion of gentian at 10 a.m. and 1.30 p.m. The patient was unaware of the addition.

Controls were performed on other subjects, all in the supine position, taking mixed maintenance diets and complying with the same ward routine.

Case.	Age.	B. P. 10 a.m. mm. of Hg.	B. P. 2.30 p.m. mm. of Hg.	Difference.
A. R.	42	124	123	- 1
E. E.	26	117	122	+ 5
A. F.	32	106	114	+ 8
A. B.	28	103	107	+ 4
R. H.	25	106	103	- 3
A. H.	43	109	108	- 1
O. L.	32	106	116	+10
B. G.	47	97	97	0
E. C.	30	128	128	0
I. F.	28	136	135	- 1
Average difference . . . . .		. . . . .		= + 2
,, extremes . . . . .		. . . . .		= +10
				- 3

So that the conclusion that  $\beta$ -iminazo caused the lowering of the blood-pressure when given by the mouth to subjects A and B is justified.

#### *Management of the Patient.*

The patients investigated had all suffered from constipation for many years and exhibited a great variety of signs and symptoms of chronic poisoning. They were kept in bed at Guy's Hospital for a week before being operated on by Sir Arbuthnot Lane. During this time a twenty-four hours' specimen of urine was obtained whilst the diet was normal, then a complete bismuth and X-ray examination of the intestinal tract was made, and finally castor oil was given preparatory to operation. During the succeeding  $2\frac{1}{2}$  days a fluid diet, from which milk was excluded, was taken, and the colon cleansed by enemata on two separate occasions. Observations on the blood-pressure were made during the period preceding the exhibition of castor oil. Ether was used as anaesthetic. Immediately after the completion of the abdominal incision a ligature was tied round the ileum at its termination to prevent any possible infection of the ileum through manipulation of the caecum. The large bowel was then freed of its attachments, a clamp placed on the ileum about 15 cm. above the ileocaecal valve, the small intestine divided at this point, and the proximal end inserted into the middle of the sigmoid flexure by an end to side anastomosis. The sigmoid was then clamped and divided above the artificial junction and the colon, together with the last coil of the ileum, removed with aseptic precautions to a sterile bowl and covered with a sterile towel. A long rubber tube was threaded through the anus and rectum into the ileum as far as 50 cm. above the anastomosis. The wounds were closed and the patient returned to bed. The rubber tube was left in position until about the fifth day; during this time the diet consisted of fluids only, milk being excluded as far as possible. About  $1\frac{1}{2}$  litres of dark green or greenish-yellow liquid drained from the tube daily. When the wound had healed completely, and the diet was normal, a further series of measurements of blood-pressure was made before the patient was allowed to leave the bed. At the same time another twenty-four hours' specimen of urine was collected and examined.

*Examination of the Ileum.*

The surface of the ileum was seared with a hot iron and the lumen opened up with sterile forceps and scissors. A generous portion of the contents was transferred on a sterile spatula to a simple, faintly alkaline isotonic saline medium containing 0.15 per cent. of histidin. This was incubated for forty-eight hours at 37° C. and any  $\beta$ -iminazo formed was estimated. In this way the conditions in the ileum were reproduced with considerable accuracy. The added ileal contents supplied bacteria in the particular combination peculiar to the patient under observation. In this way also a little cellulose and mucus were added to the medium whose reaction and saline constituents closely approximated to those found in the ileum.

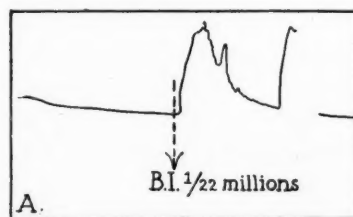
*Estimation of  $\beta$ -Iminazo.*

The method employed was that advocated by Dale and Laidlaw (2). One horn of the uterus of a virgin guinea-pig of medium weight was kept alive in a known volume of oxygenated saline at 37° C. in a Locke bath. Measured quantities of the cultures were added and the contractions of the uterus recorded by means of suitable levers. The amount of culture required to produce a strong submaximal contraction was determined and the organ standardized by noting how much of a solution of  $\beta$ -iminazo of known strength was required to cause a similar contraction. The saline used was made up with water distilled into a glass receiver and in accordance with the formula of Dale and Laidlaw.

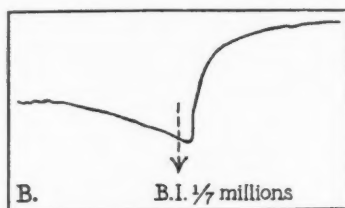
NaCl . . . . .	9.00	grm.
KCl . . . . .	0.42	"
CaCl <sub>2</sub> . . . . .	0.24	"
Dextrose . . . . .	1.00	"
NaHCO <sub>3</sub> . . . . .	0.50	"
MgCl <sub>2</sub> . . . . .	0.15	"
Water . . . . .	1000	c.c.

The magnesium chloride was added to depress the automatic rhythm of the uterus, which otherwise may become troublesome even when young virgin guinea-pigs are used.

Two types of contraction were obtained :



Produced by submaximal doses of  $\beta$ -iminazo. In this curve the summit undulates.



Produced by larger doses of  $\beta$ -iminazo. Here the summit is a straight line and the contraction is the greatest one possible.

Curves of type A alone are of use for purposes of estimation, but either type serves for the detection of  $\beta$ -iminazo.

One experiment will be described in detail and the remaining ones summarized in the form of a table.

O. L., female, aged 32. This patient had always experienced difficulty in defecating at regular intervals. When seen on June 28, 1913, she presented marked signs of chronic poisoning and of mechanical derangements in her intestinal tract. She was a black-haired woman with a deeply pigmented skin and a muddy complexion. She was very thin, almost emaciated, and nervous, greatly troubled with headaches and insomnia. The slightest exertion fatigued her and she rose late in the morning, passing most of the day on a couch overcome by feelings of lassitude. Her hands were cold and clammy. Her kneejerks were exaggerated. The breasts were the seat of chronic inflammatory changes. She was troubled by dysmenorrhoea. Her abdomen appeared rather full and was tender in most parts, but most acutely over the last coil of the ileum. She complained of flatulence and epigastric pain, which came on at irregular intervals after meals. Treatment with enemata for a period of one year and with abdominal massage for seven weeks had failed to give any relief. Bismuth was seen in the ileum eight hours after being taken. Even thirty-two hours after the bismuth meal mere traces had reached the transverse colon and none had passed the splenic flexure. (The skiagraphic examination was made by Dr. A. C. Jordan.)

Urine (reaction acid).	Before Operation. June 30, 1913.	After Operation. July 30, 1913.
Albumin . . . .	absent	absent
Sugar . . . .	absent	absent
Acetone . . . .	absent	absent
Diacetic acid . . . .	absent	absent
Bile pigments . . . .	absent	absent
Urobilin . . . .	present +	absent
Indican . . . .	present +	absent
Urorosein . . . .	present 2 +	absent
Millon's reaction (applied to Ethereal extract) . . . .	positive - +	positive - +

#### Blood-Pressure.

	Date. 1913.	10 a.m. mm. of Hg.	2.30 p.m. mm. of Hg.	
Before Operation . . . .	June 30		118	rejected, being first reading Mean 108
	July 1		111	
	July 2	106	110	
After Operation . . . .	July 30	106	104	Mean 105

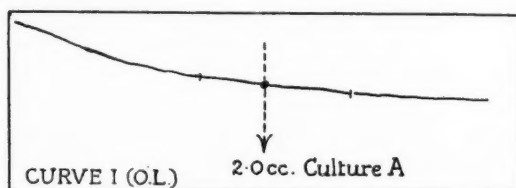


The preparation for operation consisted of castor oil, 1 oz., on July 5; a soap enema on July 6 and again on July 8. The diet was fluids only.

The operation of colectomy was performed by Sir Arbuthnot Lane on July 8.

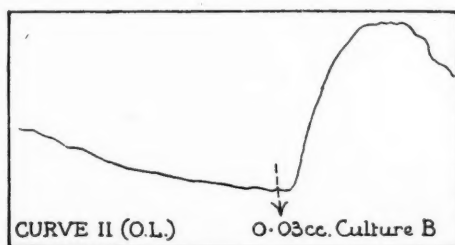
The contents of ileum were semi-solid, pale brown pultaceous pellets near the ileocaecal valve, alkaline in reaction, and yellow alkaline fluid 60 cm. above the valve: bile pigments and stercobilin in the proportion found in bile, 60 cm. above the valve; stercobilin in excess near the valve. No  $\beta$ -iminazo could be detected in the whole contents of the last 60 cm. It must be noted, however, that the patient had been starved for two and a half days.

*Bacterio-chemistry of the ileum.* A. Cultures in media containing 0.15 per cent. histidin were made from the contents found 60 cm. above the valve.



B. Similar cultures were made from the contents immediately above the valve. These were incubated for forty-eight hours at  $37^{\circ}\text{C}$ . The volume of the saline containing the guinea-pig's uterus was 225 c.c.

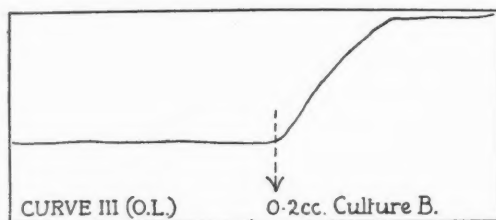
Whereas 0.2 c.c. of 0.01 per cent.  $\beta$ -iminazo (i.e. at a dilution of 1 in 11 millions) produced a strong submaximal stimulus, 2 c.c. of Culture A produced no contraction (Curve 1). Culture B was tested against two uteri;



against the first 0.01 c.c. produced no contraction, 0.03 c.c. a strong submaximal contraction (Curve 2), and 0.1 a maximal contraction; against the second uterus, 0.1 c.c. produced a maximal contraction and 0.2 c.c. also a maximal (Curve 3). Culture A therefore contained less than 0.001 per cent.  $\beta$ -iminazo and Culture B contained about 0.1 per cent.  $\beta$ -iminazo.

*Bacteriology of the ileum.* Cultures from 60 cm. above the ileocaecal valve produced no growth after three days at  $37^{\circ}\text{C}$ . in either broth agar or blood agar. At 40 cm. above the valve no growth was produced on agar after

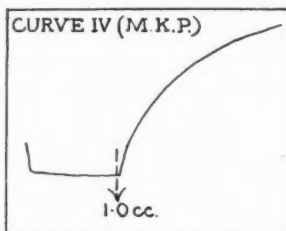
three days at 37° C. At 5 cm. above the valve a small growth of *B. coli* was seen after three days at 37° C. on agar.



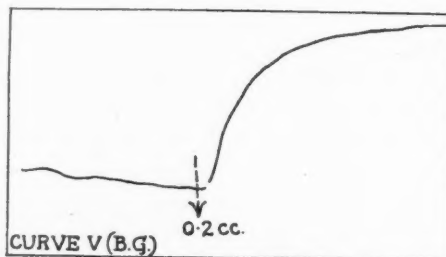
The last coil of the ileum was therefore infected with a variety of *B. coli* capable of converting histidin into  $\beta$ -iminazo; other parts of the ileum contained few, if any, aerobic bacteria.

*Summary of Cases.*

No.	Name. Sex. Age.	History.	Blood-Pressure. Before Operation.	After Operation.	Cultures.	Volume added.	Contraction produced.	$\beta$ -imin- azo in Culture.
1.	O. L. 32 Female	Cited above (see p. 434)	108	105	50 cm. above valve	2 c.c.	None	0.0 %
					5 "	0.03 "	Submaximal	0.1 %
2.	M. K. P. 46 Female	Lifelong con- stipation, se- vere symptoms 2 years	102	92	5 "	0.1 "	Small	
						0.4 "	Submaximal	0.003 %
						1.0 "	Maximal	

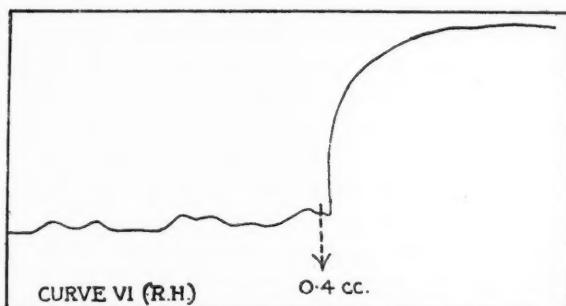


3.	B. G. 47 Female	Lifelong con- stipation, se- vere symptoms 10 years	97	—	5 "	0.1 "	Submaximal	0.01 %
						0.2 "	Maximal	
						0.4 "	Maximal	
						0.5 "	Maximal	



*Summary of Cases (continued).*

No.	Name. Sex. Age.	History.	Blood-Pressure. Before Operation.	After Operation.	Cultures.	Volume added.	Contraction produced.	$\beta$ -imin- azo in Culture.
4.	R. H. 25 Female	Lifelong constipation, severe symptoms 8 years	106	106	5 cm. above valve	0.2 c.c. 0.4 "	Submaximal Maximal	0.01 % }



5.	A. R. 42 Female	Constipated 24 years	122	101	5 cm. above valve	1.5 c.c.	0	0
6.	A. F. 32 Female	Lifelong constipation, severe symptoms 12 years	114	96	30 20 10 5	" " " "	1.5 1.5 1.5 1.5	0 0 0 0
7.	M. P. 50 Female	Lifelong constipation	140	128	5 "	2 "	0	0
8.	G. J. B. 50 Male	Constipated 15 years	132	117	5 "	2 "	0	0
9.	A. H. Female	Constipated 4 years, severe symptoms 2 years	120	108	5 "	2 "	0	0
10.	J. C. 44 Male	Constipated 1 year, very few signs of chronic poisoning	126	110	5 "	3 "	0	0
11.	E. C. 30 Female	Lifelong constipation, severe symptoms 5 years	128	102	5 "	2 "	0	0

*Analysis of these Observations.*

All the patients examined, except No. 10, exhibited signs of severe poisoning of long standing. They can be divided into two groups.

- A. Cases 1 to 4, where the blood-pressure was below 110 and the flora of whose ilea was adapted for the production of the depressor body  $\beta$ -iminazo.
- B. Cases 5 to 11, where the blood-pressure was above 110 and the flora of whose ilea was unsuitable for the production of  $\beta$ -iminazo.

The correlation of this particular type of ileal infection with the presence of a low blood-pressure lends great support to the hypothesis that many more of the symptoms exhibited by constipated patients are determined by peculiar infections of the ileum. It seems probable that if a very large number of patients were examined one would sooner or later be found with a moderate blood-pressure, say of 125 mm., and with bacilli capable of forming  $\beta$ -iminazo in the ileum. Such a one would, however, harbour pressor-forming bacilli also in the small intestine. As yet the action of the liver towards these amines has received but slight attention. Laidlaw and Ewins (3, 4) have shown that the liver destroys parahydroxyphenylethylamine, and also indolethylamine, both of which are pressor in action, but does not destroy  $\beta$ -iminazo. It therefore follows that, whether  $\beta$ -iminazo is formed alone or in conjunction with pressor bodies, the blood-pressure will be low unless the pressors are formed in such quantities that the liver cannot cope with them.

Another point brought out by these experiments is that a fall in blood-pressure always follows the operation of ileosigmoidostomy. This fall is, however, much greater in those patients whose ilea do not contain  $\beta$ -iminazo producing flora.

Group A. Average fall in B. P. = 4 mm. Maximum = 10 mm.

Group B. „ „ = 17 mm. „ = 24 mm.

This fall in blood-pressure is not a transient one, as the following data obtained from another patient will show. The flora of her ileum was not investigated, so that her case has not been quoted before.

K. McC., female, aged 44. Constipated since the age of 14. After lying in bed for three days her blood-pressure was on two successive occasions 133 and 143 mm. respectively. Three weeks after colectomy, the wound having healed by first intention, her blood-pressure was 102 and 90 mm. Six months later she was seen again in perfect health. The blood-pressure was taken whilst she was sitting in a chair and under the influence of the excitement of her visit. It now was 124 mm.

Mean before operation (recumbent) 138 mm.

Mean three weeks after operation (recumbent) 96 mm. } Fall = 14 mm.

Mean six months after operation (sitting) 124 mm. }

I wish to suggest that a very great variety of micro-organisms may be present in the intestinal canal, each capable of accomplishing a specific series of chemical reactions: that these organisms can only be clearly and rationally

differentiated by investigation of their chemical powers, and that some of the symptoms of toxæmia in constipated subjects are determined by the particular selection of organisms which have infected the stagnant contents of the ileum. The condition of the blood-pressure has been taken as a simple example.

#### SUMMARY.

1. The presence of bacteria in the ileum capable of forming  $\beta$ -iminazo from histidin has been correlated with the appearance of the vascular signs of chronic poisoning by  $\beta$ -iminazo in the same subjects.

2. In constipated subjects the lower portions of the ileum would seem to furnish a suitable site for the production of poisonous intermediate bodies of bacterial activity.

(a) The flora is increased to an abnormal degree, although it is still restricted in its variety.

(b) Products of proteolysis are present and their passage through the ileocaecal valve is often delayed for several hours.

(c) The mucous membrane is specially adapted for processes of absorption.

3. The conditions in the colon would appear to be favourable for completely destructive processes and the formation of innocuous end-products:

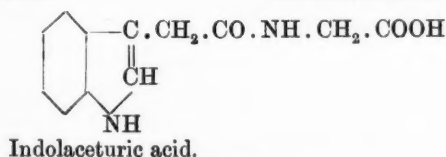
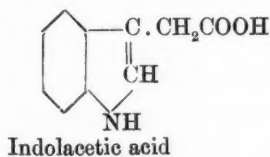
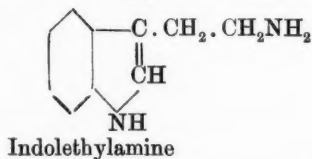
(a) The flora is immeasurably rich.

(b) The ileal effluent remains in the colon for many hours.

(c) The mucous membrane is not adapted for processes of absorption to the same extent as that of the small intestine.

#### *Urine of Constipated Subjects.*

Unfortunately the fate of  $\beta$ -iminazo in the organism is not yet known, but ultimately it may be possible to correlate three factors—the intestinal flora, the low blood-pressure, and the presence of the as yet unknown end-product in the urine. A few details, however, are known of the fate of indolethylamine. It is converted into indolacetic acid by the liver and excreted either as such or in combination with glycine as indolaceturic acid.



These substances are easily detected in the urine by adding to it one-third of its volume of strong hydrochloric acid and a drop of dilute sodium nitrite, or by warming with hydrochloric acid and a drop of nitric acid, or simply by allowing to stand overnight after the addition of hydrochloric acid. Under any of these conditions a red pigment—*urorosein*—develops, insoluble in chloroform but readily soluble in amyl alcohol, and showing a well-marked absorption band in the green with a spectroscope. On acidification the colour is discharged, but alkalis restore it. This substance is not present in the urine of constipated individuals as frequently as is *indican*, but I have found it in moderately large amounts in two urines out of twelve examined and in detectable quantities in many others. *Indolacetic acid* is isolated by saturating the urine with ammonium sulphate, rendering it acid in its reaction to Congo red and extracting with ether. In this way an extract was obtained which showed a very strong *urorosein* reaction, but there was not sufficient material for the isolation of *indolacetic acid*. *Indolaceturic acid* is best extracted with acetic ether, and the solubilities of the precursor of *urorosein* in the urines which were examined corresponded more closely with those of *indolaceturic acid* than with those of *indolacetic acid*.

It would appear from the foregoing data that possibly a bacillus may be detected in faeces which has a specific action on tryptophane, producing *indol-ethylamine*; that this bacillus is present in the ilea of those patients whose urines show strong *urorosein* reactions, but not in other ilea.

Research has also been done in connexion with the fate of *parahydroxy-phenylethylamine*. It is converted into *parahydroxyphenylacetic acid* by the liver and excreted as such in the urine. Urine containing this substance reacts strongly with Millon's reagent. It may be extracted from acidulated urine with ether. Normal urine gives a slight reaction with Millon's reagent, but the compounds responsible are insoluble in ether. Urine obtained from constipated patients occasionally shows these reactions; that is to say, it contains substances soluble in ether which react strongly with Millon's reagent and are presumably allied to *hydroxyphenylacetic acid*. Possibly a specific bacillus converts tyrosin to *hydroxyphenylethylamine* in the ilea of those constipated subjects who excrete ether-soluble compounds which react with Millon's reagent.

Another abnormal substance which is very frequently found in the urine is *urobilin*. Its significance is not quite clear. Possibly it may indicate derangements of liver function, the result of the deleterious action of a constant stream of poisons from the alimentary tract. It disappears from the urine almost immediately after the performance of *ileosigmoidostomy* and does not appear again even after a lapse of several years.

The four tests, namely, for

- |               |                                    |
|---------------|------------------------------------|
| 1. Urobilin,  | 2. Indican,                        |
| 3. Urorosein, | 4. Hydroxyphenolic bodies (Millon) |

form a very useful index of bacterial decomposition of the small intestine,



# FORMATION OF $\beta$ -IMINAZOLYLETHYLAMINE IN THE ILEUM 441

although they cover a very small proportion of the reactions which probably occur. They may be applied not only in constipation and portal congestion arising from any cause, but also to determine the site of infection in some forms of anaemia, progressive nephritis, and rheumatoid arthritis, where the laws of chance would lead one to suspect a primary lesion in the ileum in a certain proportion of cases. If they are always carried out in the same way, a rough estimate may be formed of the relative amounts of the bodies present. In this research the following conventions are adopted:

A twenty-four hours' specimen of urine is diluted until the specific gravity = 1015, and 50 c.c. are taken for each test;

Negative reaction . . . . .	= -
Doubtful . . . . .	= (+)
Definite . . . . .	= +
Strong . . . . .	= 2+
Extreme . . . . .	= 3+

1. *Urobilin*. 50 c.c. of urine are made acid with glacial acetic acid and extracted with 10 c.c. of amyl alcohol. If a definite absorption band can be observed through 3 cm. of fluid, i.e. in an ordinary 100 c.c. cylinder, urobilin is present. As a confirmatory test a saturated solution of zinc acetate is added to the amyl alcoholic extract, when a green fluorescence indicates the presence of urobilin:

Very faint spectrum . . . . .	= (+)	
Distinct absorption band . . . . .	= +	
Very dark band . . . . .	= 2+	
If the amyl alcoholic extract is of a dark sherry colour and considerable dilution is necessary before the spectrum can be seen, urobilin . . . . .		= 3+

2. *Indican*. To 50 c.c. add 25 c.c. of concentrated hydrochloric acid and 10 c.c. of chloroform. Add a dilute solution of sodium hypochlorite, a drop at a time, shaking and allowing the urine to stand for about five minutes between each addition. Continue until no more blue pigment is produced:

Very faint blue with chloroform . . . . .	= (+)
Definite pale blue . . . . .	= +
Sky blue . . . . .	= 2+
Dark blue-black . . . . .	= 3+

3. *Urorosein*. To 50 c.c. add 25 c.c. of concentrated hydrochloric acid and 2 drops of 1% sodium nitrite. Shake with 10 c.c. of chloroform to extract indigo pigments, then extract the residual pigments with 10 c.c. of amyl alcohol and examine with a spectroscope:

Very faint absorption band . . . . .	= (+)
Definite band . . . . .	= +
Very dark band . . . . .	= 2+

If the solution is of a deep crimson colour and considerable dilution is necessary before a spectrum can be seen, urorosein . . . . . = 3 +

4. *Hydroxyphenols*. To 50 c.c. add 5 c.c. of 25 per cent. sulphuric acid and extract with 15 c.c. of ether. Evaporate the ether and add 2 c.c. of water and 2 c.c. of Millon's reagent. Boil repeatedly and allow to stand :

Pale rose . . . . . = +  
 Dark red . . . . . = 2 +  
 Deep mahogany brown . . . . . = 3 +

If Millon's reaction is applied directly to urine even normal urine gives a pale red coloration = +.

These tests were applied to a series of urines with the object of noting whether the formation of decomposition products could be diminished by ileosigmoidostomy. Such reduction would support the claim that the products arise from abnormal bacterial action in the small intestine.

*Series 1. Constipated patients taking a normal diet.*

	Urobilin.	Indican.	Urorosein.	Millon.
1	+	2+	—	—
2	(+)	+	—	—
3	—	2+	—	—
4	+	2+	—	—
5	+	+	—	—
6	—	—	2+	—
7	+	+	2+	+
8	—	—	—	—
9	+	+	—	—
10	+	—	+	—
11	—	2+	—	+
12	—	2+	—	+
Total	7+	14+	5+	3+

*Series 2. Patients with ileosigmoidostomy. (Operation two to forty-eight months ago.)*

	Interval since Operation.	Urobilin.	Indican.	Urorosein.	Millon.
1	28 months	—	—	—	—
2	24 "	—	—	—	—
3	17 "	—	—	—	—
4	12 "	—	—	—	—
5	48 "	—	2+	—	+
6	14 "	—	—	—	—
7	17 "	—	—	—	—
8	5 "	—	+	—	—
9	36 "	—	—	—	—
10	2 "	—	+	—	—
11	29 "	—	—	—	+
12	8 "	—	—	—	—
Total		0	4+	0	2+

## FORMATION OF $\beta$ -IMINAZOLYLETHYLAMINE IN THE ILEUM 443

It is quite evident that the production of these bodies can be greatly diminished simply by overcoming the delay in the small intestine even when the colon is left in the abdomen as a large blind sac of faeces.

*Series 2.* Cases 1 to 6 and 8 to 12, colon left *in situ*.

„ „ Case 7, colon removed.

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## FAMILY CEREBRAL DEGENERATION WITH MACULAR CHANGE (SO-CALLED JUVENILE FORM OF FAMILY AMAUROTIC IDIOCY)

By FREDERICK E. BATTEN

With Plates 35-38

### *Introduction.*

CERTAIN forms of progressive cerebral degeneration occurring in children of one family are generally recognized. That described by Waren Tay and Sachs under the title of 'Family Amaurotic Idiocy' has received careful pathological investigation and is the best known. Continental observers (Vogt (24), Bielschowsky (3), and others) recognize a late infantile and juvenile form of amaurotic idiocy without the distinctive macular changes, and on pathological grounds they assign all these cases to one group, namely hereditary degenerative disease. Jendrassik and Higier have, on clinical grounds, contended that there is no essential difference between the various forms of familial disease.

A rare form of progressive cerebral degeneration occurs in children during the first decade of life, and these cases have been described under the title of 'Cerebral Degeneration with Symmetrical Changes in the Macula' by Mayou (2), Batten (1), and others. Nettleship (12), in his paper 'On Cases possibly allied to Tay's Infantile Retinitis', refers to these. Spielmeyer (19) described a form of cerebral degeneration occurring in the children of one family associated with blindness. The children in this family were healthy till six years of age; they then showed mental deterioration, epileptic fits occurred, and the children died at the age of puberty. Four of the five children were affected, only the eldest escaping. Failure of vision, due to optic atrophy and a profuse retinal atrophy of the type retinitis pigmentosa sine pigmento, was present. Syphilis as a factor could not be excluded, for it is possible that the father contracted syphilis after the birth of the first child. On pathological examination the Betz cells of the cerebral cortex showed a destruction of the cell body, the processes remaining more or less normal.

Mülberger (11) describes two cases of a similar nature in a boy and girl aged  $3\frac{3}{4}$  and  $1\frac{1}{2}$  years respectively; both children were living at the time of the report.

(Q. J. M., July, 1914.)

H. Vogt (24), under the title 'Über familiäre amaurotische Idiotie und verwandte Krankheitsbilder', describes a form of family cerebral diplegia with blindness, and progressive dementia which does not commence during infancy but in the later years of childhood. The family which he records resulted from six pregnancies. The mother and father were healthy, and there was no evidence of syphilis. The following is the family tree:

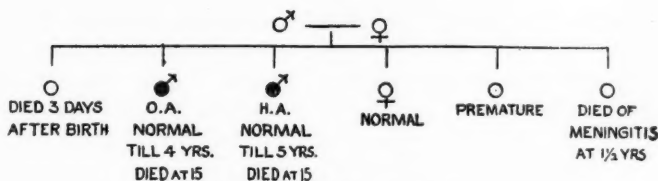


FIG. 1. Chart of the V. Family.

The first boy, O. A., was normal till four years old, he then began to degenerate. He had learnt to walk at eleven months, and to talk at one and a half years. He gradually lost these faculties, became blind, irritable, and, lastly, apathetic. He died when fifteen years old. The autopsy showed nothing abnormal in the brain macroscopically; the convolutions were not small, and there was no dilatation of the ventricles. The brain weighed 980 grm.

The second boy was normal till five years old; learnt to walk at one year old, and to talk in his second year. Failure of sight began when he was five years old, and an attempt was made to teach him in the blind school. His intelligence, however, became more and more impaired and school had to be given up. Epileptic fits first occurred when ten years old, but he only became completely paralysed a year before his death, which took place when fifteen years old. Macroscopically the brain showed no change, but on microscopical examination a primary degeneration of the ganglion cells was found with changes similar to those found in family amaurotic idiocy. Vogt gives the following as a typical clinical picture of the disease. A hitherto healthy child (usually more than one in a family without any special race disposition) becomes ill during the school age, sometimes between the age of fourteen and fifteen. The children in the same family become affected in the same year of life. The beginning is gradual; the first symptom is usually the failure of sight, but loss of mental capacity or motor weakness may first appear. The loss of sight passes in the course of months to a complete blindness. Ophthalmoscopically there is atrophy of the papilla. The mental development stands still, or goes back. The children do not progress in the school, soon lose the acquired capacity to read and write, and, lastly, of speech. They become unsocial, dirty in eating, unclean in habits, and totally inattentive to their surroundings, no longer know their own mother or make articulate speech. Little by little they become completely demented. Hand in hand, in most cases, there is diminution of motor function, at first weakness in the limbs and back, later complete paralysis. The paralysis is some-

times flaccid, sometimes spastic, leading to complete helplessness, atrophy, and death.

The parallelism of the clinical symptoms with the Waren Tay cases is clear. The agreement lies in (1) the familial character and the absence of syphilis, (2) the symptoms, and (3) the course. The difference lies in (1) the absence of race proclivity, (2) the absence of characteristic macular change, and (3) the difference of age.

Bielschowsky (3), in a paper entitled 'Über spät-infantile familiäre amaurotische Idiotie mit Kleinhirnsymptomen', gives an account of a family of three children, a boy and two girls, not of Jewish race. The mother had only these three children; there had been no miscarriages and the Wassermann reaction was negative both in parents and in children. There was a marked history of epilepsy both on the mother's and father's side, but strongest on the mother's side. The parents themselves were free from epilepsy.

In all three children the illness began at the fourth year of life, up to which time the development had been normal. The eye symptoms developed relatively late, the failure in intelligence being the first and motor weakness the last symptom. In the final stage the children became completely paralysed, the arms hung flaccid by the side, and when the child was placed in a sitting position the head fell upon the chest. In the two older children the disease lasted three and a half and four years respectively. At the autopsy the dura mater appeared normal, the pia mater was thickened, and the brain weighed 670 gm., which is said to be about 230 gm. less than the normal. The frontal convolutions approached the normal, but the further posteriorly one went the more atrophic were the convolutions. Gross abnormalities of the convolutions and sulci were not present. The cerebellum was unusually small, not only in its absolute mass but also in its relation to the large brain. The microscopical examination showed some change in the pia mater, swelling of the pyramidal cells in the cortex, with changes similar to those described by Schaffer in the Tay-Sachs disease. The Nissl granules had disappeared from the cell body, but were not replaced by the usual fine granulation. The calcarine region showed the most marked degeneration, with glia cell proliferation; no changes were seen in the vessels. In the cerebellum the cells of Purkinje showed the same form of degeneration, as did also the ganglion cells of the spinal cord.

Lüttge (8), in a paper entitled 'Über einen besonderen pathologischen Befund aus dem Gebiete der frühinfantilen familiären Erkrankungen des Nervensystems', describes a similar condition in two infants of a mother whose two brothers were stated to have suffered from the same disease.

Karl Schaffer (16), in a paper entitled 'Beitrag zur Nosographie und Histopathologie der amaurotisch-paralytischen Idiotieformen', describes a case in a girl, aged 19 in 1895, who died at the age of 24 with progressive mental defect, defective eyesight, in whom no gross changes were found in the brain, but extensive ganglion cell degeneration. Schaffer suggested that this case corresponded to the juvenile form of amaurotic idiocy.



Schaffer (17), in a paper entitled 'Zur anatomischen Wesensbestimmung hereditärer Nervenkrankheiten', sums up as follows:

(1) The hereditary degenerative diseases (H.D.D.) affect primarily the hyaloplasm of the neurons.

(2) The so-called fibrillae play no part in the cytopathology of the H.D.D.; the Nissl granules only a secondary part. The H.D.D. may be designated as affection of the non-differentiated protoplasm of the neuron.

(3) The affection of the hyaloplasm may be either a hypertrophy or an atrophy; the qualitative factor in H.D.D.

(4) The affection of the hyaloplasm can be general or local, the difference producing the variations in the form of the H.D.D. This is the quantitative factor in the H.D.D.

(5) The affection of the hyaloplasm may be rapidly progressive, leading to death in a short time, or so slowly progressive that the length of life is little or not at all affected. This is the intensity factor in H.D.D.

Weber (23) has described a family amaurotic idiocy without characteristic ophthalmoscopic signs. Autopsy was performed in one case, but no microscopical examination is recorded.

Darier (4), in a paper entitled 'Progressive Familial Macular Degeneration', gives an account of five cases of macular degeneration occurring in two families, and refers to the published cases with and without cerebral degeneration. He says that it is probable that the more precocious the macular changes the more likely are the cerebral functions to be affected—when the eye symptoms do not appear till twelve to fourteen years the brain is not affected.

Other forms of progressive cerebral degeneration occurring in children may be mentioned, but no advantage is gained by associating them with the above cases.

Progressive lenticular degeneration affects several members of a family, but it rarely occurs in children, and the earliest case on record is that of a child aged 10.

Pfaundler and Schlossmann (15) refer to a diffuse 'brain sclerosis' which is not congenital but develops in a child in the best of health and leads to complete dementia. They do not refer to this as a familial affection.

Pelizaeus and Merzbacher (14 and 10) describe a scattered degeneration of medullated fibres of the brain as a family affection, but the condition is essentially congenital and rarely progressive.

H. Vogt (25), in a paper entitled 'Tuberöse Sklerose', describes progressive dementia with epilepsy in children, and Paul Schuster (18), under the title 'Beiträge zur Klinik der tuberösen Sklerose des Gehirns', recognizes this as a familial disease.

*Classification.*

From the above digest it is clear that there is a group of cases showing progressive cerebral degeneration which do not correspond to the clinical features as originally described in the family amaurotic idiocy of Waren Tay and Sachs. It is these cases which it is proposed to discuss in this paper, and for this purpose the following division is suggested:

(1) Family amaurotic idiocy—Waren Tay-Sachs.

(2) Juvenile progressive cerebral degeneration, with amaurosis with or without macular and retinal changes—Spielmeyer (19), Mülberger (11), Vogt (24), Bielschowsky (3), Mayou (9), Batten (1, 9), and cases described in this paper.

It is well recognized, as Jendrassik (7) and Higier (5) have pointed out, that there is in all probability no hard and fast line between the various types of hereditary degeneration; unless, however, some form of classification based on a clinical foundation is adopted it is very difficult to form a clinical picture of the various cases which arise, and a classification should assist in a more accurate investigation, both clinical and pathological, of cases of this nature as they come under observation.

It has been shown that the pathology of some of these cases of hereditary degeneration, which present different clinical features, is similar, and it seems probable that they may be due to the same toxin, either endogenous or exogenous, and that the variation of symptoms is dependent on variations in age, race, &c. The exact nature of the toxin has yet to be proved.

*Clinical Features.*

The family about to be described presents symptoms of cerebral degeneration which correspond to the second division, namely, juvenile progressive cerebral degeneration with amaurosis and with macular changes.

## FAMILIAL CEREBRAL DEGENERATION, MACULAR CHANGES

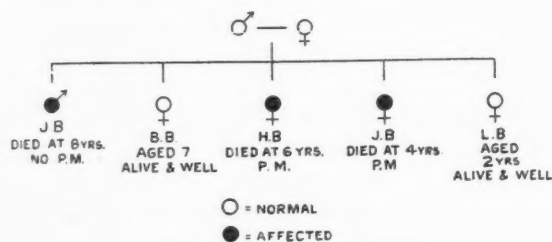


FIG. 2. Chart of the B. Family.

The family consisted of five members, one male and four females. The mother and father were perfectly healthy and normal individuals; they were not related, not Jews, and no history of mental defect existed in any of the collaterals.

The mother had four brothers and four sisters, five of whom were married and had children who were perfectly healthy; the father had one sister married but without children. The father had two brothers; one died of pneumonia, the other by accident, at the ages of 18 and 22 respectively. The eldest child, a boy, James B., 3 years 10 months, was in May, 1909, admitted to the Hospital for Sick Children under the care of Mr. Waugh, suffering from epilepsy. It was stated that three months previously he had been run over and suffered from a scalp wound on the vertex. He was unconscious, and was kept in the district hospital for three weeks after the accident. Since that time he had on various occasions suddenly fallen down and had convulsive movements of all his limbs. He had become irritable and constantly dirty in his habits since the accident; previously he was occasionally dirty. On August 10, 1909, Mr. Waugh trephined the boy and turned down an osteoplastic flap and exposed the whole area of the scar. The skull and dura mater appeared perfectly normal, and after opening the dura there appeared to be a slight excess of the subdural fluid, and the cortical veins were congested; otherwise nothing abnormal was noticeable. The boy recovered from the operation, but still continued to scream loudly and was in much the same condition as before the operation. No examination of the cerebrospinal fluid was made. He was discharged from the Hospital, and died in February, 1913, when 8 years old, having slowly passed into a demented condition. No autopsy was made.

The second member of the family, Bertha B., aged 7 in 1914, was physically and mentally a normal child, and on examination nothing abnormal could be discovered. She was said, however, to have had nocturnal incontinence.

The third member of the family, Hilda B., was well until the age of  $3\frac{1}{2}$  years. She was born at full term, in normal labour without instruments, cut her first tooth at five months, walked at twenty months, and began to talk about the same time. She had her first fit when  $3\frac{1}{2}$  years, and since that age had had frequent fits, had gradually lost power in the limbs, had become mentally defective, had become dirty in her habits, and took but little notice of her surroundings.

On examination in June, 1913, she lay in bed with her legs extended; when placed in the erect position she stood on tiptoe, but could not walk. She failed to grasp objects with her hands, but could move her arms in all directions; she was unable to talk, and had attacks in which she screamed loudly. The pupils reacted well to light, the child could follow a light, the optic disks were pale, the vessels were normal and no change could be seen in the fundus. The knee-jerks were active, the plantars both gave extensor responses, abdominal reflexes were present. The cerebrospinal fluid was quite clear and normal in character. The Wassermann reaction was negative both in the blood and in the cerebrospinal fluid. The child remained in hospital for about four weeks, but practically showed no change during that time. The fits were controlled by small doses of hyoscin. The child was discharged from the Hospital in June 1913, and readmitted to Hospital in February 1914. She was then emaciated, had rigidity of arms and legs, took no notice, did not see, but the pupils still reacted to light. The optic atrophy was more marked, and at the maculae there was a fine pigmentary degeneration with considerable disturbance of the pigment in the periphery of the fundus (Fig. 3). The knee-jerks were brisk, ankle clonus was present, and both plantars gave an extensor response. The child died on March 7, 1914, and a post-mortem was made which showed a normally convoluted brain with shrunken convolutions. The microscopical appearance of the brain and eyes in this case will be dealt with in a subsequent paper.

The fourth member of the family, Jessie B., aged 3 years and 10 months, was said to be quite well up to six months previously. She was apparently a normal child in every respect till three; she learnt to walk and talk and was clean in her habits. Fits occurred about the age of three years and recurred with increasing frequency, and she had passed into a condition

showing marked mental defect. She, like her sister, had frequent attacks of screaming, could just support her weight on her legs, but could not stand or walk. The pupils reacted quite well to light, the disk and fundus of the eye were quite normal. The limbs could be moved in all directions, the knee-jerks were active, there was no ankle clonus, both plantars showed an extensor response, and the abdominal reflexes were active. The cerebrospinal fluid was perfectly normal and the Wassermann was negative in both blood and cerebrospinal fluid. This child contracted chicken-pox and died in September, 1913, aged 4 years.

A post-mortem was performed by my house physician, Dr. Moodie, and it is the changes in the brain of this child which are about to be described.

The fifth member of the family, Lily B., aged 2 years and 6 months, is alive and perfectly healthy. She talks and walks quite well for a child of her age. The knee-jerks are present, and the optic disks and fundus are normal. The grandmother believes that this child is going to be affected because of a slight turning out of the left foot.

*Pathological Examination of J. B., the fourth member of the above family.*

Nothing abnormal was observed in regard to the membrane or the surface of the brain. The thoracic and abdominal viscera were normal. After hardening in formalin the pia mater was removed and the brain examined. The convolutions were well formed (Fig. 4) and nothing abnormal could be detected either on the surface, base, or in cut sections of the brain or cerebellum. The liver and spleen also appeared normal, both macroscopically and microscopically.

Microscopical examination of the nervous system was carried out by the Weigert-Pal, Marchi, Nissl, van Gieson, and Bielschowsky methods.

*Marchi method.* Section of the cerebral cortex from the upper portion of the precentral gyrus showed a considerable amount of degeneration in the fibres of the white matter streaming down from the cells of the cortex, but very little degeneration could be seen in the grey matter (Fig. 5). The degeneration from the precentral gyrus could be traced into the medulla and spinal cord. Sections taken from the frontal, post-central, and occipital region of the cortex show comparatively little degeneration by this method.

In the *cerebellum* similar degeneration could be seen in the fibres of the white matter passing from the grey matter of the cortex (Fig. 6). The cells of Purkinje appeared to be diminished in number and those present stain rather darkly with the Marchi method.

In the medulla there was considerable degeneration in the pyramidal tract, in the transverse fibres, and also in the intramedullary portion of the cranial nerves.

In the cervical, dorsal, and lumbar region of the spinal cord there was a diffuse degeneration not only in the pyramidal tract, but also in the antero-lateral tract and posterior column.

There was some degeneration in the ventral roots and a few degenerated fibres could be traced to the cells of the anterior horn. The dorsal roots show but little change.

*Weigert-Pal method.* The medullated fibres of the cortex were well stained, and the tangential fibres of the cortex appeared to be about normal. No abnormality was to be seen in the spinal cord stained by this method. The cerebellum showed some diminution of the medullated fibres. Sections of the optic chiasma showed but little change, as did also sections of the optic nerve. The eyes of this case were unfortunately not preserved.

*Van Gieson method.* No change could be detected in the vessels, either in the brain or spinal cord, by this method and no inflammatory reaction was present. The membranes of the brain and cord appeared normal.

*Nissl and v. Gieson method.*—*Cerebrum.* Sections of the cortex taken from the upper portion of the precentral gyrus stained by the Nissl and v. Gieson methods showed very marked changes in the pyramidal and Betz cells (Fig. 7). The cells were few in number; some were small in size, others swollen, and many of them showed an excentric nucleus and vacuolation and diffuse staining of the chromatophilic substance, which tended to arrange itself around the nucleus.

*Cerebellum.* The Purkinje cells were diminished in number, had lost their dendritic process, were swollen and vacuolated. Some had central nuclei, but the cell body was poorly and diffusely stained (Fig. 8). Compare this with Fig. 9, normal cerebellum prepared and stained in a similar manner. A layer of large granular cells was very marked in the region of the Purkinje cells. The deeper granular layer was very poor in cells. Stained by the Bielschowsky method similar changes were shown (Fig. 10). Compare this with Fig. 11, normal cerebellum cortex.

*Spinal cord.* The cells of the ventral horn of the spinal cord were numerous and showed changes similar to those above described, but compared to the cells of the cerebrum and cerebellum were well preserved.

#### *Summary.*

An account is given of a family of five children, three of whom were affected with a progressive disease leading to dementia, blindness, and paralysis, one of whom showed changes in the macular region of the eyes. The children were healthy at birth and developed in a normal manner till the age of  $3\frac{1}{2}$  years. Epileptic fits then occurred and they began to degenerate. They became noisy, dirty in habits, and developed a spastic condition of the limbs. Death ensued in the one child at the age of eight, in the other at four, and in the third child at six years. All three of these children have died, and in two a post-mortem has been performed. In one case no change was visible in the nervous system macroscopically, in the other only slight atrophy, but on microscopic examination diffuse degenerative changes affecting the ganglion cells were visible in the cerebrum, cerebellum, and spinal cord. The Wassermann reaction of the blood and cerebrospinal fluid was negative in both cases, and no change in the brain or membrane was found suggesting congenital syphilis.

Another family of progressive cerebral degeneration was seen in 1905, but it has not been possible to trace the subsequent history of these two cases.

*Fred B.*, seven years old in 1905, was the first of two children, and was, according to his mother's statement, well till three and a half years old, when he began to lose the power of walking. He gradually lost the power of talking, and since six years old has not been able to talk at all. He lost the power of sitting up, became dirty in his habits and blind.

Instruments were used at birth; he walked when eleven months old, but never talked well. He had one fit when one and a half years old.

At seven years old he was demented, took no notice; was blind, dribbled, had a general tremor of head and limbs and lay in bed with arms and legs rigid in the flexed position.

The knee-jerks were active, there were double ankle clonus and extensor responses.



Ophthalmoscopic examination showed optic atrophy and a curious pigmented condition of the whole fundus with irregular white patches. No definite change at the macula. (Mr. Herbert Parsons's report.)

*Henry B., 4 $\frac{3}{12}$ .* Henry, like his brother Fred, was apparently normal till about three and a half years old, when he had an epileptic fit. These fits recurred about one a week, and the boy passed into a condition of mental defect. He was noisy, lost the power of talking, and became unsteady in his gait.

On examination he was restless and irritable, he could walk unsteadily. He seemed to see; the pupils reacted to light; no atrophy or change could be seen in the fundus similar to that found in the case of the elder child. The knee- and ankle-jerks were present and the plantars were flexor.

The boy was too noisy to be kept in the hospital. The cerebrospinal fluid was not examined and no Wassermann test was made (1904).

#### *Conclusions.*

It is clear from a consideration of the cases just recorded and of those which have been described by Vogt, Bielschowsky, and others, that there is a form of familial cerebral degeneration which occurs at a later age, has no race proclivity, and somewhat different clinical manifestations from that described by Waren Tay and Sachs under the title of 'Family Amaurotic Idiocy'. The typical features in these cases are *loss of intellectual faculties, loss of vision, loss of motor power.*

In some cases all three defects seem to start together and run an equal and concomitant course. In other cases the mental symptoms first appear, the visual and the motor symptoms remaining long in abeyance.

In other cases, again, the visual symptoms appear first, motor and mental symptoms following later or not at all.

In some cases the degeneration begins in early life, in others in later infancy, in others, again, in early youth.

Some cases pass rapidly to a fatal termination, others are slow in their progress.

Some cases show very distinct changes in the macula, others pigmentary changes in the retina, which are not limited to the macula. Others, again, show no fundus change, or do so only in the later stages of the disease.

Clinically there is a great variation in the symptoms, and this, together with their time of appearance, forms a basis for classification. Pathologically these cases are essentially the same, and the changes in the cells are strikingly similar in all cases which have come to autopsy.

The clinical division suggested in the body of the paper is tentative, but it seems well to have some such division for the purpose of describing the various forms of familial progressive degenerations which occur in children.

It is proposed to deal with the macular and retinal changes in a subsequent paper, and especially in regard to their relation to the cases described by R. D. Batten, Stargardt, Darier, and others.



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## DESCRIPTION OF FIGURES.

PLATE 35, FIG. 3. Hilda B., 5½ years. Fundus of right eye to show the pigmentary degeneration which occurs at the macular region; a similar appearance was present in the left eye.

FIG. 4. Lateral view of the brain of Jessie B., aged 4 years, showing the normal appearance of the convolutions.

PLATE 36, FIG. 5. Cerebral cortex, precentral gyrus, of Jessie B. stained by Marchi's method, showing degeneration of the medullated fibres passing from the cells of the cortex.

FIG. 6. Cerebellum of Jessie B. stained by Marchi's method, showing degeneration of the medullated fibres passing from the cells of the cortex.

FIG. 7. Cerebral cortex, precentral gyrus, of Jessie B. stained by Nissl's method, showing the chromatolytic changes in the Betz and pyramidal cells. The drawing is a composite one in that all the cells figured do not occur in the single field of the microscope. Magnified 800 diameters.

PLATE 37, FIG. 8. Cerebellum of Jessie B. stained by the Nissl method, showing chromatolytic changes in the cells of Purkinje and loss of the dendritic processes. Note the increase of compound granular corpuscles around the cells of Purkinje and the diminution of the cells of the granular layer. Compare with the normal cells of Purkinje and granular layer seen in Fig. 9.

FIG. 9. Normal cerebellum stained by Nissl's method, showing cells of Purkinje, dendritic processes, and granular layer; for comparison with Fig. 8.

PLATE 38, FIG. 10. Cerebellar cortex of Jessie B. stained by Bielschowsky's method, showing the degenerate condition of the Purkinje cells, the absence of dendrites, and the layer of large granular cells in the region of the Purkinje cells.

FIG. 11. Normal cerebellar cortex stained by Bielschowsky's method for comparison with Fig. 10.



FIG. 3

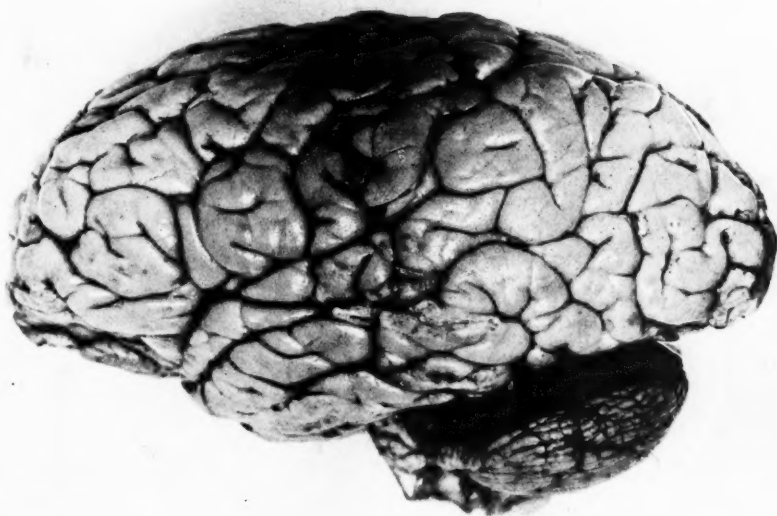


FIG. 4



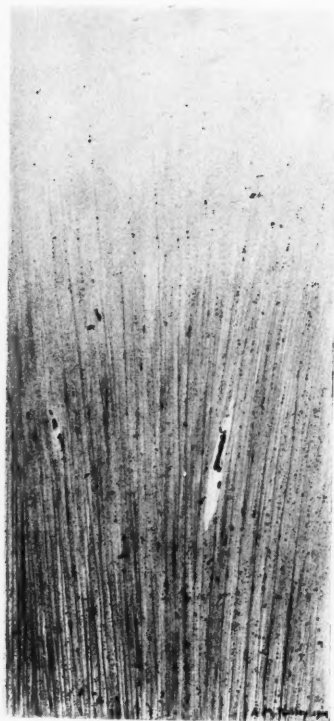


FIG. 5

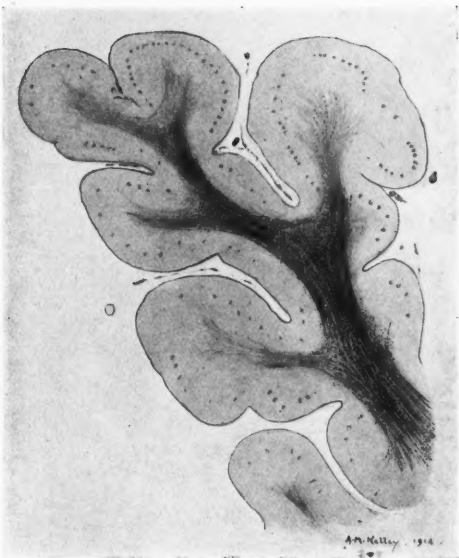


FIG. 6

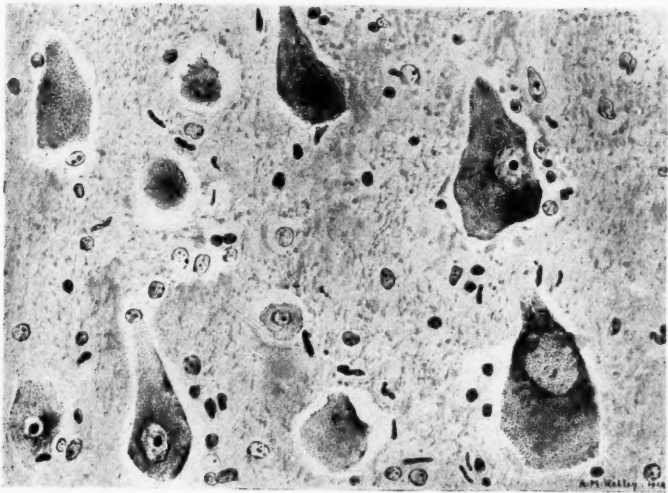


FIG. 7





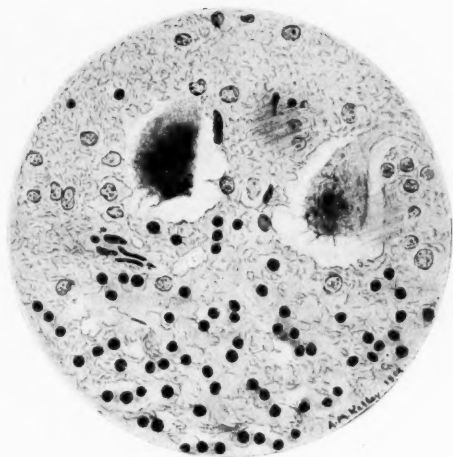


FIG. 8

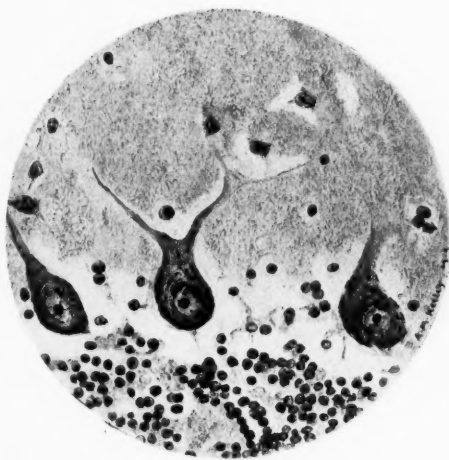


FIG. 9



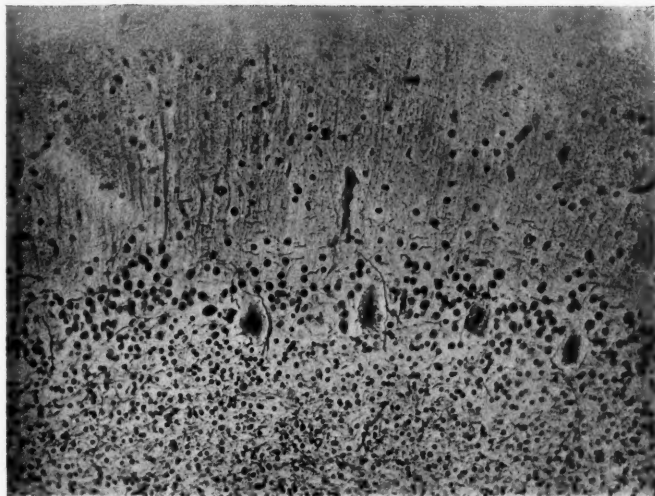


FIG. 10

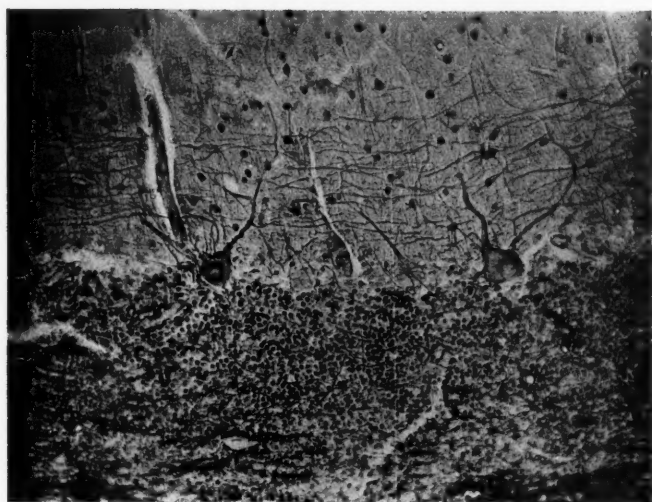
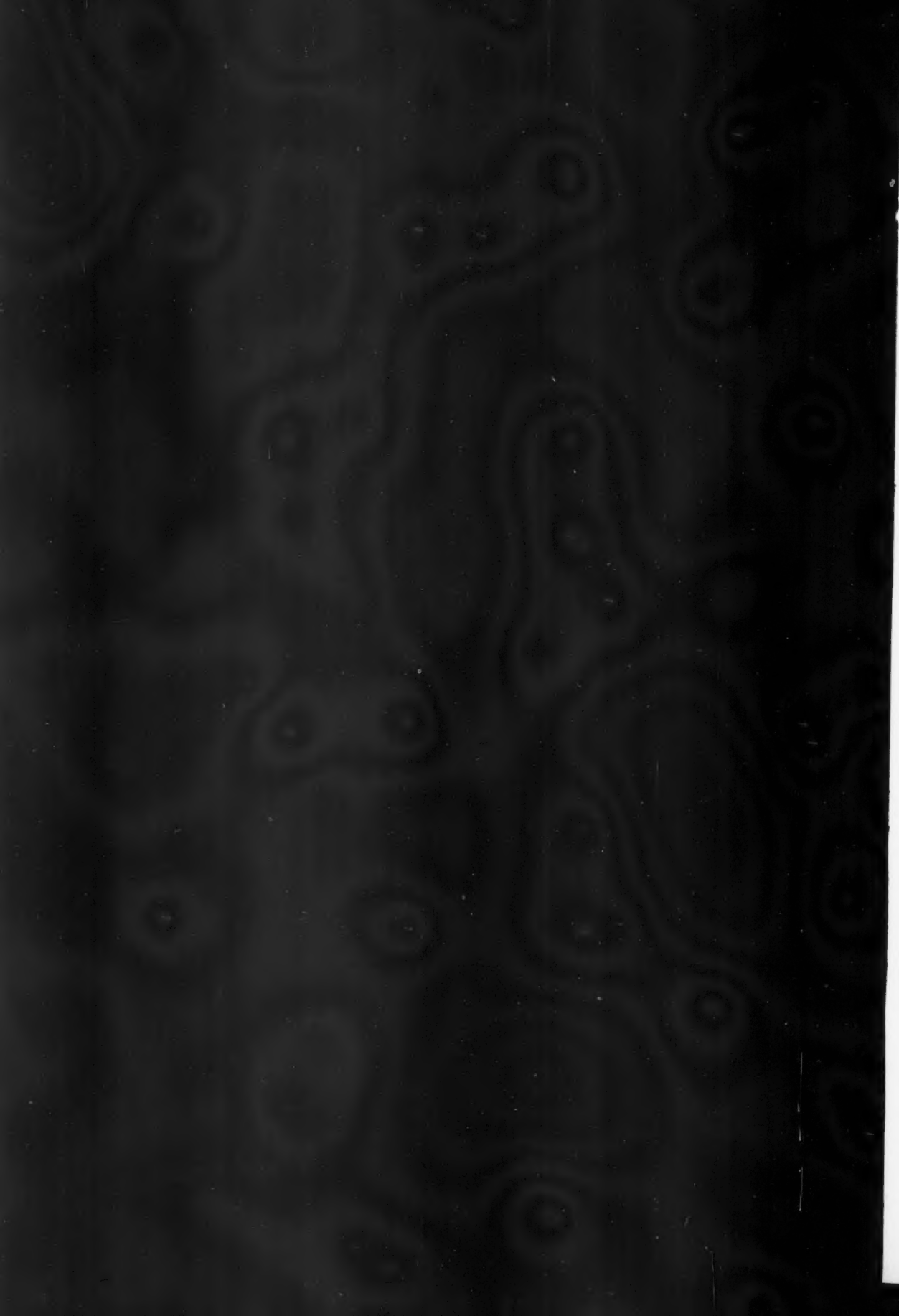


FIG. 11



## CRITICAL REVIEW: THE DIAGNOSIS OF PANCREATIC DISEASE

By ARTHUR F. S. SLADDEN

A REVIEW of the present state of knowledge of the diagnosis of pancreatic disease is likely to be of use to those who have interest in the subject, for the volume of work done in this connexion of recent years is very large, and the great importance of the pancreas in medicine and surgery has become more marked than ever before.

The inaccessibility of the gland to clinical observation, the difficulties of experimental work, and the somewhat unemphatic post-mortem appearances of the gland in the commoner forms of its disease have all tended in the past to obscure the vital importance of the pancreas in the economy of the body.

Modern physiology, pathology, and bio-chemistry have all combined to place the gland in its true position, but much remains to be done before its exact physiology can be established, and diagnosis of its pathological conditions be rendered sure.

The history of the pancreas is eloquent of the baneful effect of dogmatic authority on any scientific subject. According to P. Lazarus, Eudemus four centuries B.C. described the pancreas as the source of a digestive juice supplied to the intestine, but six hundred years later this was forgotten, and Galen's view of the gland as a 'cushion' for the support of the stomach and large vessels held sway even after the time of the great anatomists of the sixteenth century, Vesalius and Fallopius. In 1642 came Wirsung's demonstration of the main duct of the pancreas, but even then the true significance of the gland was not realized until the classical researches twenty years later of René de Graaf upon the nature and use of the pancreatic secretion. Then apparently a reaction set in, and for a time the pancreas tended to be regarded as the root of all evil, including many mental troubles; as Bonet said, '*Succus pancreatis plurimos morbos facit*'.

Very little advance in knowledge of this organ was made until the work of the great experimental physiologists of last century, Claud Bernard and many others. From their researches the importance of the pancreatic secretion for digestion of proteins, fats, and carbohydrates was firmly established. In the second half of last century the clinical pathology of pancreatic disease

hardly kept pace with the advances in physiology and pathological anatomy, nor can it be said that this aspect of the subject is even now on a level with the latter.

The next great step forward in the knowledge of the pancreas was the epoch-making work of von Mering and Minkowski to prove the association between the pancreas and diabetes, thus opening up the way to later developments in the conception of internal secretory activities. The output of work on the pancreas in the last five-and-twenty years has been very great and many summaries and reviews with full bibliographies have been compiled.

It is not my intention to give a full bibliography with this review; references to the subject run to many hundreds and are easily accessible in Oser's and Körte's works of 1898. Claessen's book in 1842 gave the earlier work, and for more recent researches the monographs of Albrecht, Albu, K. Glaessner, and F. Frank can be readily consulted.

The study of the pancreas from almost every point of view is beset with difficulties. The physiologist debates over its mode of innervation and the biochemist over the character and identity of the ferments formed within it. A long battle has been waged over the so-called island cells of Langerhans, and even now the issue is hardly settled; in fact a recent suggestion (Milne and Peters) that the islet cells are resting acinal cells which take on an internal secretory function seems to be perilously near to a compromise which gives all the essential points to the opposite party.

The part played by the gland in the complex interactions of the internal secretory activities of the body is by no means clearly allotted, nor can its influence upon carbohydrate metabolism be satisfactorily defined. The pathology of the pancreas is therefore not likely to be a barren ground for speculation or research for some time to come.

In spite of the difficulties enumerated, much advance has been made, and notably within the last decade, so that the practical clinician seeking the aid of physiology and pathology can gain considerably more help towards the diagnosis, treatment, and prognosis of pancreatic disease than was the case a dozen years ago.

It may be said at the outset that the diagnosis of abnormalities of this gland resolves itself largely into a question of laboratory methods; even the most mature and sage clinician is bound to utilize such means to supplement simple clinical examination of the patient before he can pronounce with any confidence that there is pancreatic disease.

There is no infallible criterion of the presence of pancreatic disease either amongst simpler bedside observations or amongst the most painstaking tests devised for laboratory use. Nor is this surprising, for the functions of the gland are complex and not fully understood, and its activities numerous and obscure.

Two other sources of difficulty have also to be met. There is much evidence accumulated to prove that many, if not all, of the functions of the



pancreas may be undertaken by other glands within the body provided that the call on their services be not too sudden. Secondly, it is very rare to find disease of the pancreas pure and simple, and the correct assessment of the influence of secondary features of the disease is one of the main problems to be faced. Jaundice, for instance, or increased peristalsis, acidosis, malnutrition, anaemia—any of these may obscure the diagnosis by their effect on the clinical picture, or by producing anomalous results in a pathological test which, if it could be applied 'clean-cut' as it were, would give an equally precise and accurate answer.

Such confusion of the issue is of course a daily phenomenon in nearly every branch of medicine, but it appears to be especially a feature of pancreatic disease; while the first difficulty mentioned, the power of compensatory action which may develop in presence of pancreatic insufficiency, is displayed to an unusual degree in certain cases of disease of this gland. Cases of atrophy of the pancreas are recorded in which the digestive functions were carried on satisfactorily; a notable instance of this is the case reported by Glaessner and Sigel in 1903, where there was well-marked steatorrhoea. Five years later the same patient under the care of Keuthe showed perfectly normal fat absorption by careful analysis, although at post-mortem there was found almost complete atrophy of the pancreas. In such a case as this, one is driven to conclude either that compensatory activity developed in other of the digestive organs, or that there were accessory pancreatic nodules. Such accessory glands are not very rare. Serra reported an example, and Carwardine and Short have collected nearly forty cases.

Keuthe's case has further interest as exhibiting the different degrees to which functions ascribed to the pancreas may be affected by disease. The case gave evidence of insufficiency of trypsin and nuclease in the alimentary canal, and of some impairment in carbohydrate metabolism, so that in spite of normal fat digestion other functional tests were suggestive of pancreatic disease, which indeed was present to a marked extent.

In considering the question of diagnosis the clinical aspect claims, as it always should, first attention. Except in some advanced cases of malignant growth of the head of the gland, clinical examination of itself is not often able to render possible a confident diagnosis of pancreatic disease. More often it leads the experienced clinician to suspect the gland and to proceed to further investigation in order to make certain of the diagnosis. Of course, long experience combined with a happy clinical instinct may in the more pronounced surgical cases fairly often lead to a diagnosis which proves correct, but the most experienced clinicians, physicians and surgeons alike, are probably in this matter the most ready to avail themselves of any aids which recent research can offer.

The subjective symptoms vary greatly, but deep-seated epigastric pain not controlled by taking of food and sometimes observed to radiate to the left shoulder-blade is fairly commonly found, whilst French authors describe

a 'pathognomonic point' (von Ehrmann) so many centimetres above the umbilicus! Diarrhoea or more often frequent and copious stools are a common accompaniment—in fact Tileston considers 'massive' stools to have diagnostic importance, the weight of dried faeces in pancreatic cases being sometimes as much as five times the normal. Wasting and anaemia are frequently found as a result of impaired assimilation. Jaundice is associated in many cases with pancreatic disease, sometimes as a preceding condition, more often as a corollary due to pressure on the common bile duct as it lies within the head of the pancreas.

The close relationship of the common bile duct and the orifice of the duct of Wirsung has very important results in practice, and Mayo-Robson more than ten years ago insisted upon the surgical importance of this anatomical arrangement, showing how an impacted gallstone may easily lead to pancreatitis and all its consequences. Ochsner lays stress upon the presence of tenderness over the middle of the right rectus muscle in cases of pancreatitis, and mentions also having noticed in some advanced cases peculiar circumscribed areas of fat in roll-like masses on the front and sides of the chest and abdomen.

The chemical characteristics of the faeces considered later on often give valuable information; routine examination of the urine, if it discloses glycosuria, may give a very definite lead. Other features are often noticed, but can hardly be regarded as peculiar in any way to pancreatic disease. Indican, for instance, is commonly found in the urine of pancreatic cases, but as a result of associated conditions, such as enteritis, colitis, and intestinal fermentation. Bile also may be found when the common duct is involved, and its appearance may be of use in realizing the progress of fibrosis or carcinoma of the head of the pancreas. Urobilinuria has similar significance and is due not to pancreatic disease as such, but to hepatic or biliary involvement. The 'acetone bodies' also may be associated with pancreatic disease, but only when the preceding glycosuria can be proved to arise from pancreatic lesion can they be regarded in any sense as a sign of pancreatic disease.

There is very little evidence in favour of the view advanced by de Dominicis that in pancreatic disease the excretion of urinary phosphates is increased; at least one may say that very careful metabolism experiments would be required to establish this theory. It is interesting to note, however, the observation of Falta that the secretions of the accelerator group of glands seem to stimulate phosphate secretion, so that withdrawal of the depressor influence of the pancreas might work in the same direction.

Calcium oxalate crystals have also been regarded as a sign of pancreatic disease, and Cammidge in particular considers that the frequency of their presence is due to more than coincidence, and that a fundamental disturbance of calcium metabolism in pancreatic disease may lead to excessive oxalate excretion, and also favour deposition of salts of calcium within the pancreas. Lazarus states that oxalic acid is not normally present in pancreatic juice, nor does there seem any evidence that oxalates take any special share in the forma-

tion of pancreatic stones. The influence of the pancreas, if any, on oxalate excretion is therefore more likely to be exerted by some metabolic path. For my own part, I have found no evidence for an oxaluria peculiar to pancreatic disease, and even if such disease should favour oxalate deposit in the urine there are so many other commoner causes of the same condition that no diagnostic aid is likely to be derived from it.

Such signs and symptoms may lead the clinician to suspect the condition of the pancreas and to proceed to functional tests in the endeavour to establish a correct diagnosis.

It is convenient to consider tests of pancreatic sufficiency under two headings:

1. Tests of the external secretion, dependent upon the presence or absence of ferments of the pancreatic juice.

2. Tests dependent upon other functions of the pancreas.

Generally speaking, the tests under the first heading are made on material obtained from some portion of the alimentary tract, whether stomach, duodenum, or rectum, whereas most of the second are made with the urine. The adrenalin mydriasis test of Loewi, a simple bedside test, will be discussed separately. From the practical standpoint the various urinary tests are simpler to carry out, and so may appeal more strongly to clinicians. Their theoretical basis, however, is often more obscure than that of the tests of external secretion. It may be of help to append a detailed list of the more important methods here considered.

1. Tests of external secretion, dependent upon abnormalities in the ferments of the pancreatic juice:

- Oil-test breakfast.

- Duodenal intubation.

- Glutoid capsule test (Sahli).

- Tests of nucleo-protein digestion (Schmidt, Kashiwado, Fronzig).

- Azotorrhoea.

- Creatorrhoea.

- Tests for tryptic power of faeces (Müller and Schlecht, Gross).

- Steatorrhoea.

- Analyses of fat in faeces.

- Tests for lipolytic power of faeces.

- Palmin test-meal (von Ehrmann).

- Tests of diastatic power of duodenal contents.

- Tests of diastatic power of faeces.

- Estimation of lecithin in faeces.

- Effect of administration of pancreatic preparations.

2. Tests dependent upon other functions of the pancreas

- The simpler characteristics of the urine.

- Ferments in urine—Diastase.

Pentose derivatives in urine (Cammidge).

Glycosuria, actual or potential.

Adrenalin mydriasis (Loewi).

The proteolytic power of pancreatic juice was very fully established by the researches of Claud Bernard (1855) and others, and for the investigation of pancreatic functions many methods have been devised to test the tryptic power of the secretion. Owing to the difficulty of obtaining pancreatic juice pure and direct from the patient all the methods are liable to error or misapprehension. If the trypsin be collected from the stomach after regurgitation through the pylorus, as in the oil-test breakfast, the gastric acidity introduces a source of error. Collection of duodenal juice direct, although achieved by Einhorn and others, does not appear to be a method to commend itself to the patient. Later down the intestinal tract the secretion of erepsin and the formation of proteolytic enzymes of bacteriological origin introduce confusing factors, and finally, in examining the faeces for trypsin, the rate of passage of the intestinal contents and perhaps also their composition both form possible sources of grave error. Nevertheless, tests to ascertain tryptic efficiency, despite the pitfalls in the way, have attracted a great amount of attention and some degree of success.

#### *The Oil-test Breakfast.*

The oil-test breakfast depends upon the observations of Pawlow and Boldyreff that the feeding of oil into an empty stomach causes a regurgitation of duodenal contents through the pylorus. The method was worked out for clinical application by Boldyreff in 1904 and later by Volhard, and full details may be found in the latter's paper. Objections have been urged against the method on the score of interference from leucocytic or carcinoma ferments, and from erepsin and perhaps from gastric juice. Long and Muhlemann in a paper published this year describe experiments which seem to show a retarding effect of normal gastric juice upon both amylolytic and tryptic activity. This retardation is more marked where the proportion of uncombined hydrochloric acid is greatest. Volhard's method, however, takes account of the possibility of hyperacidity of the stomach.

Frank regards the test as valuable to prove a complete achylia pancreatica, or if a series of tests be made on one patient, to gain useful information as to the tryptic function of the pancreas. In von Ehrmann's case (1910) of chronic pancreatitis the oil-test breakfast was successful, and Mahlenberg too favoured this method and rarely failed to find trypsin unless there was complete absence of pancreatic juice. A full account of the subject was given by Michailow in 1912, who collected 450 cases, in nearly 400 of which trypsin was demonstrated in the test-meal result; his analysis of the cases where trypsin was absent is not altogether convincing as evidence for the value of the test for diagnosis.

The possibility of failure to regurgitate is always present. Michailow insists that it is important for the patient not to retch, no easy thing to secure after swallowing about five ounces of olive oil neat. Finally, the laboratory test occupies two or three days for its completion, not always a convenient interval. Nevertheless the method seems worth an extensive trial, and the technique is relatively simple.

#### *The Method of Duodenal Intubation.*

Of all the tests dependent upon examination of the external secretion of the pancreas, this method, associated with the name of Einhorn, is the most excellent in theory, for if any examination for pancreatic ferments is to be successful, one using the pancreatic juice obtained direct from the duodenum should certainly be the best.

Various devices have been tried for securing a sample of the secretion in the duodenum. One of the earliest was due to Hemmeter and Kuhn, consisting of a wide tube to be passed into the stomach to act as a guide for a narrower sound to be introduced into the duodenum, a method not without danger to the patient and requiring great skill and experience. Later came Einhorn's device, a small metal capsule enclosed in gelatin and attached to a soft fluffy string of known length. This capsule was swallowed an hour after a light meal and left in the intestinal tract about three hours, or all night. The position of the capsule was best checked by X-ray examination, and in favourable cases on withdrawal it was found to contain duodenal juice. Contamination by saliva, gastric juice, or mucus was always possible, and the optimum quantity of juice obtainable was but small, and so the method could only be regarded as useful to demonstrate the presence of trypsin rather than its absence.

An advance from this method has been made by using a metal capsule attached to a long rubber tube, allowing the patient to swallow the capsule, and waiting for the peristaltic movements of the stomach to pass the capsule on into the duodenum. From time to time aspiration of the tube is made to ascertain whether the capsule has passed the pylorus. X-ray examination is a most desirable adjunct for this purpose. In favourable cases the duodenum is reached and from 5 to 10 c.c. of clear duodenal juice may be obtained. Frank obtained juice in fourteen cases out of twenty-four, but his results are hardly sufficient to throw much light on the value of the method for diagnosis of pancreatic activity.

There are many sources of failure possible; pyloric spasm, retching and vomiting, 'spiralling' of the tube within the stomach, and unsuitable temperament in the patient may all prevent the securing of juice. Moreover, if a successful aspiration is achieved, the examination of the juice may be rendered abortive through contamination with gastric secretion. From the work of Long and Muhlemann it does not appear that HCl of itself destroys tryptic activity



to any great extent, but when associated with pepsin, 'free HCl' causes a distinct retardation of tryptic activity. Further, from the work of Chace and Myers it seems that the normal variations in the activity of the pancreatic enzymes are so great, that any method dependent upon direct examination of the pancreatic secretion is only of value for establishing the existence of a complete achylia pancreatica, or perhaps, in the absence of bile, to prove a complete obstruction of the bile duct; this, however, can be achieved by simpler methods. In 1909 Kleineberger spoke against this process, and two years later Oskar Gross inveighed strongly against it as useless and dangerous. Other Germans, however, had some success; Junghans, for instance, obtained juice in 60 per cent. of cases and von Barth-Wehrenalt in 55 per cent., whilst Frank's results have already been quoted.

The method has also been investigated considerably in America, and some success has there attended trials. In addition to the authors already mentioned, Crohn has used duodenal intubation extensively with fairly encouraging results, securing some quantity of juice in nearly 90 per cent. of his cases. A. F. Hess has reported a case of much interest: in an infant of seven weeks there was congenital obliteration of the bile ducts; successful duodenal catheterizations proved the existence of normal secretions in the duodenum, and a post-mortem examination later on revealed a duct of Santorini in an anomalous position giving complete pancreatic compensation, while sections of the gland were quite normal.

Undoubtedly when duodenal juice is successfully obtained the method has value for acquitting the pancreas of disease. A failure to find trypsin has not the same value for the diagnosis of a pancreatic lesion, so many other causes may lead to this failure. From the standpoint of the practical clinician the method is open to serious objections; patients do not appreciate spending the night, or even a few hours, with a tube down the oesophagus, nor does the risk of injury to stomach or duodenum, where ulceration already exists, seem entirely remote.

#### *Sahli's Test.*

The test invented by Sahli is perhaps the best known, as it is one of the earliest of the functional tests for pancreatic disease, dating from 1897, and further it has the advantage of simplicity and ready clinical application. Gelatin capsules are made and hardened in formalin by a process of which the exact details are not given by the author. The capsule is filled with iodoform; salicylic acid or methylene blue powder and other substances have also been used as indicators. According to Sahli the hardened capsule is not soluble in gastric juice, but on meeting a normal pancreatic secretion solution takes place and the contents of the capsule are set free to be absorbed. In a normal subject this should take place within four hours, and a test of the urine with appropriate reagents should reveal traces of the encapsulated material. If iodoform be used,



the saliva should react with starch and acid to show presence of iodide. If there is no evidence of absorption of the contents of the capsule within five hours the test is regarded as indicating pancreatic insufficiency. But the difficulty of excluding gastric stasis, and the fact that the reaction in normal persons is frequently delayed, make the value of the test very doubtful.

Sahli thinks that if the gastric condition is found to be satisfactory and peristalsis is normal, the test has significance for diagnosis. Most of the German authors regard it as unreliable, perhaps owing to the difficulty of hardening the capsule uniformly and sufficiently; Pratt quotes one case, of a patient with carcinoma of the head of the pancreas and occlusion of the ducts, where the test indicated normal pancreatic secretion, and another where there was to every appearance a normal gland, but the reaction was delayed many hours. Ferreira introduced a modification, giving encapsulated salicin, but as the nature and origin of the ferment which splits salicin is not known the method merely includes a further objection to those met with in the simpler test of Sahli.

#### *Schmidt's 'Beef-cube' Test.*

Amongst the earlier tests devised is that of Schmidt, the administration of small cubes of beef muscle hardened in alcohol and wrapped in silk gauze to aid identification of the cubes in the faeces. It was thought that the digestion of the nuclei could only take place by the action of 'nucleases' of pancreatic origin, so that recognition of undigested nuclei in the muscle fibres recovered from the stools would point to deficiency of pancreatic secretion. Fronzig recently has borne out Schmidt's view of nucleolytic action of pancreatic juice, in a series of *in vitro* experiments, but Barbour maintains that the succus entericus may contain nucleases, not to mention enzymes of bacterial origin with nucleolytic powers. The rate of passage of the intestinal contents is certainly a disturbing factor and the evidence for the reliability of the method is not very convincing. Tileston says that it only helps in total occlusion of the pancreatic duct, and then is superfluous! An indeterminate result is very common, and the process of finding the muscle fibres in the stools is neither easy nor inviting.

Modifications of Schmidt's test have been introduced by Kashiwado and by Fronzig. Kashiwado's method consists in the administration of specially prepared nuclei isolated from the thymus gland of the calf. Schmidt and Frank both regard the method as an improvement, but to a large extent the same objections already raised against Schmidt's test hold. As stated in my own paper, it seems probable that if diarrhoea can be excluded a positive outcome of the test may be of help, but a negative result is hardly to be trusted: a positive result, moreover, is only likely to be obtained when the pancreas is practically completely out of action.

Of Fronzig's method I have no experience, but it seems to have much in common with Kashiwado's test: in any case it is open to the same fallacies.

He uses as a source of nucleo-protein the nucleated red cells of the blood of frogs or geese, mixing the defibrinated blood with barium sulphate, which acts as an indicator in the faeces which have to be searched for undigested red corpuscles. It is noteworthy that Wohlgemuth, van Westenrijk, and Glaessner and Popper have all denied the presence of a nucleolytic ferment in the pancreatic juice, but Fronzig's work seems to contravene this denial.

#### *Azotorrhoea.*

The term azotorrhoea is used to denote an excessive excretion of nitrogen compounds in the faeces, the inference being made that such compounds are present owing either to failure of digestion of proteins or to failure of absorption of products of digestion.

The determination of the nitrogen content of the faeces is a process only to be undertaken by a skilled chemical pathologist, and as a clinical test it is ruled out in ordinary conditions of practice. Moreover, to place such determinations upon a sound basis a complete metabolism experiment has to be made, with estimations of nitrogen intake and output.

As with all other investigations of the proteolytic activity of pancreatic juice, the disturbing effect of other ferments, pepsin, erepsin, and proteolytic agents of bacterial origin, complicate and obscure the issue; while on the other hand, disease of the absorbing areas of the intestine, tuberculous ulceration, or degeneration and atrophy of the mucous membrane may lead to deficient absorption of nitrogen products which have not suffered from lack of pancreatic juice to break them down. This being so, one can hardly agree with Barbour that azotorrhoea is a cardinal sign of pancreatic disease except with the proviso that the mechanism of absorption in the small intestine is not deranged.

A review of work done on this subject shows quite unmistakably that azotorrhoea is a common feature of pancreatic disease. Deaver, Tileston, Pratt, von Ehrmann, O. Gross, Barbour, and Brugsch have all communicated cases in point, whereas there appear to be few records of completely normal utilization of nitrogen in presence of definite pancreatic disease: Delfino has published a case of pancreatic cyst where this was so.

A very interesting feature in most of the cases recorded is the influence of extracts of pancreatic gland to improve nitrogen absorption. Von Ehrmann's patient (1910), with chronic pancreatitis and a loss of nitrogen equal to 43 per cent. of the intake, when given pancreatin lost only 17 per cent. of the nitrogen in the diet given, and this an increased intake. In an interesting and valuable series of observations on two cases, one with chronic pancreatitis without icterus, the other with icterus the result of syphilitic cirrhosis, the same author found the nitrogen loss in the pancreatic case was 34 per cent. of the intake, that of the icteric case, 12 per cent. Pratt's account of seven cases with pancreatic disease showed a great increase of nitrogen loss, from the normal 5 per cent. or 10 per

cent. to 30 per cent. or 40 per cent., and animal experiments confirmed this. He quoted Tileston for cases of icterus with carcinoma of the pancreas where loss both of fat and nitrogen was increased; that icterus alone, however, has but little influence on nitrogen absorption is shown by Ehrmann's case above mentioned and by Brugsch's experience that with uncomplicated icterus the nitrogen loss may be 11 per cent., but with a pancreatic lesion added it will rise to 33 per cent.

Brugsch makes an interesting suggestion that in cases where acidosis is present, as in advanced diabetes, this may reduce the alkalinity of the duodenal and intestinal contents and so impair ferment activity and lead perhaps to an augmentation of fat and nitrogen excretion. There does not appear to be any experimental work in support of this theory, but against it can be adduced the experiments of Long and Muhlemann, who showed that *in vitro* trypsin can withstand an acidity of more than 0.3 per cent. HCl for half an hour at 40° C. If pepsin be present also a distinct retardation of tryptic activity is caused. Their experiments also showed that commercial preparations of pancreatic gland rapidly deteriorate below the pharmacopoeial standards. In two cases reported by O. Gross doses of 20 tablets daily of Pankreon (Rhenania) produced no effect on nitrogen absorption, but by doubling the dose a marked benefit was obtained. By the use of raw pig's pancreas, 75 grammes per day, an even better improvement occurred. Cammidge's experience of new gland as compared with dry preparations is similar, and Mosenthal in a case of glycosuria with creatorrhoea, steatorrhoea, and absence of trypsin in the stools gave Pankreon without effect, but on substituting 150 grammes of raw sheep's pancreas very great improvement, both in fat and protein digestion, took place, so much so in fact that acidosis tended to increase.

Although other and simpler tests render observations on nitrogen loss in the stools a rather unsatisfactory method for diagnosis, nevertheless it is probably true that pancreatic insufficiency is the most usual cause of azotorrhoea, and if metabolism experiments be undertaken with observations on the influence of pancreatic preparations on nitrogen absorption, much valuable information can be gained both for diagnosis and the direction of treatment. Tileston (1912) regards determinations of nitrogen loss as quite as valuable for diagnosis as fat determinations, and in absence of intestinal disease impairing absorption he regards a nitrogen loss of more than 30 per cent. as being strongly suggestive of pancreatic disease.

#### *Creatorrhoea.*

A natural corollary of azotorrhoea if the patient is on an ordinary diet is the microscopic finding of undigested muscle fibres in the faeces, readily recognized by their striations and yellowish colour. This phenomenon has been known for many years; it has been called creatorrhoea and is very simple to recognize, since in a film of *normal* faeces examined under the microscope it is rare to find more than one or two muscle fibres in a field, and most often they are entirely absent.

According to Kleineberger the finding of creatorrhoea is about the best evidence for pancreatic insufficiency; Wertheimer concurs, as does von Ehrmann, who stipulates, however, that the patient's meat ration for a few days previously should not exceed two ounces daily. He compared the effect of giving pancreatin upon azotorrhoea and creatorrhoea, and came to the conclusion that the effect was quantitative, not qualitative, i. e. there was still impaired digestion of muscle fibre, although the digestion of nitrogenous food as a whole was so improved that the nitrogen loss became normal. In a later paper (1913) von Ehrmann still maintains this view, which has also been confirmed by Oskar Gross. How this apparently selective action of pancreatic extract comes to pass is not at all clear; Albu, arguing from a case of carcinoma of the duodenum with complete occlusion of the pancreatic duct, in which no creatorrhoea could be found, suggested the possibility of an internal secretion of the pancreas taking an essential part in the digestion of muscle fibres. In Barbour's case and in my own experience administration of pancreatic extract may clear up a creatorrhoea, and in any case it appears a policy of rather doubtful utility to call in a fresh internal secretion to account for observations otherwise 'unexplained'.

Creatorrhoea is not free from fallacies—diarrhoea or even rather abnormal peristalsis may lead to appearance of muscle fibres in the faeces, and Albu states that a condition of achylia gastrica may produce a similar result. If these possibilities are excluded a finding of creatorrhoea has great positive significance. A negative observation has not, however, the same value for the exclusion of pancreatic disease, although, as Pratt remarks, in cases where pancreatic insufficiency has been definitely excluded well-marked creatorrhoea has not been observed. K. Glaessner drew attention to the possible action of proteolytic enzymes of intestinal or bacterial origin, to render a negative observation of less value for diagnosis.

#### *Tryptic Power of Faeces.*

So many disturbing factors have to be considered in dealing with tests devised to show the amount of trypsin in the faeces, that methods invented for this purpose have given little satisfaction. The influence of erepsin and proteolytic ferments of leucocytic or bacterial origin have to be discounted—no easy matter, for the exact difference between trypsin and erepsin, if any, is not yet defined in a satisfactory way. Of the various methods invented to measure the tryptic power of the faeces, those of Müller and Schlecht and of O. Gross may be mentioned. Müller and Schlecht plate out a portion of the stool rendered alkaline, on serum agar. The plate is sterilized at 60° C. to inhibit bacterial growth, and any ferments present are allowed to act on the serum for twenty-four hours, tryptic activity being marked by characteristic areas of liquefaction. Hirschberg obtained very good results by this method, but others have not found it so satisfactory.

Other methods are based upon digestion of solution of casein with alkaline extract of faeces. Volhard's was the earliest, but that most often used is the method of Oskar Gross. One part of faeces is extracted with three parts of 1:1000 soda solution and filtered. One part of this filtrate is added to five parts of a  $\frac{1}{2}$  per thousand alkaline solution of casein, and after addition of chloroform the mixture is incubated at 38° C. The progress of digestion is tested by adding a drop of acetic acid to the test-tube. After complete digestion no precipitate forms on rendering the fluid acid, and the degree of turbidity produced is in inverse ratio to the degree of activity of the ferment in the faeces. The procedure is simple and the test has received considerable support from workers in Germany, and in this country from Cammidge. Gross is enthusiastic over his test, and even claims that from the slowing of the rate of digestion of the casein the degree of pathological involvement of the pancreas can be gauged—would it were so!

Pratt relates the case of a man, apparently normal, whose faeces four times examined did not digest casein. On the other hand, one may quote the example of a case of bronzed diabetes (this Journal, Jan. 1914), where with cirrhotic pancreas nevertheless there occurred a normal digestion of casein by the faecal extract.

Apart from the possible effect of proteolytic ferments not of pancreatic origin one must not overlook the question of re-absorption of ferments, especially where there is much intestinal stasis or constipation. Many individual trials, for and against the utility of tests for tryptic power in the faeces, are on record, and unfortunately in some instances bias or prejudice appears to warp judgement.

Recent work by Liftschütz on this subject is helpful. He finds no essential difference in the action of trypsin, erepsin, and bacterial ferments upon proteins, but finds no action of erepsin on egg albumin. The action of bacterial ferments on casein is the same in quality as that of trypsin but not so powerful, and so a test by Gross's method with negative outcome (enfeebled digestion of casein) is more reliable than a positive result. On the other hand, his experiments seem to show that a high tryptic activity of faecal extract is strong evidence for a healthy pancreas. Liftschütz advocates a control test with Mett's tubes containing egg albumin, especially as he finds erepsin without action on these. Matko, in the same journal, relates favourable experiences with Gross's casein method so long as certain precautions of diet and aperients are observed. He refers also to the presence of antitrypsin in the blood serum, previously described in 1909 by Schlecht and Wiens. Matko defers description of his method, but states that the quantity of antitrypsin in the blood serum runs parallel with that of trypsin in the faeces, and that icterus alone does not cause diminution of antitrypsin in the blood.

An independent research by an Italian observer, Zuccola, gives perhaps the fairest opinion, that an examination of ferments in the faeces is a useful aid in the diagnosis of pancreatic efficiency when taken in conjunction with other methods. It is not absolute in its indications, nor does it yield results which



can be regarded as quantitative. As with so many other functional tests of pancreatic activity, a positive outcome pointing to absence of trypsin has more value than a negative result, especially in view of possible interference from other proteolytic enzymes.

#### *Steatorrhoea.*

The question of fat digestion and excretion looms large in the history of the study of pancreatic disease. The clinical recognition that obvious excretion of fat in the stools was often associated with disease of the pancreas dates back nearly a century to Kunzmann; Richard Bright, in the *Transactions of the Medico-Chirurgical Society of London* for 1833, described several such cases, and in the same volume are given other instances of excretion of fat in the faeces in such quantity as to be readily recognized by the unaided eye. To such a symptom, the most marked sign of impaired fat assimilation, was given by Kunzmann the name *steatorrhoea*, and of recent years this convenient term has come into very general use.

F. Müller in 1887 showed the important influence of bile for the process of fat assimilation, and developed the view that when *steatorrhoea* was present in pancreatic disease there was always a concurrent jaundice. This, coming from so eminent an authority, undoubtedly tended to obscure the real relationship of the pancreas itself to fat digestion, especially owing to the frequency with which jaundice is associated with a pancreatic lesion, and when also one reviews the very discordant results obtained by workers in this field up to the present day, one finds less cause for surprise that a sign in which Bright predicted there would be found much diagnostic significance, even now awaits its complete explanation.

The term *steatorrhoea* may now be held to include the passage of fat in the stools to an extent recognizable as excessive only by microscopic aid. Nor is this mode of examination always reliable, and a more exact control by chemical analysis is a more satisfactory method. Nevertheless, for clinical purposes a microscopic examination of a thin film of faeces often gives evidence of the state of fat excretion, although the findings cannot be considered as more than roughly qualitative. It has to be remembered that a normal stool may contain from 20 to 30 per cent. of fat, and experience and a uniform technique are necessary for getting reliable results. Wertheimer recommends the giving of a standard diet containing 100 to 125 grammes of butter for a couple of days before a microscopic examination of the faeces. Staining with Sudan III or with iodine I have sometimes found helpful, and Lohrisch recommends staining with Nile blue as giving good differentiation. One is more likely to fail in the direction of missing an excess of fat: if the total fat percentage is over 40, a microscopic *steatorrhoea* is almost sure to be evident.

The microscopic appearance of fatty stools may vary; often the fat particles



are very finely subdivided and admixed with the rest of the excreted matter. If, as is often the case in 'pancreatic' stools, the proportion of fatty acid is very high, a characteristic rancid smell is noticed; in a few instances, and these the most striking, the fat separates out like cream on milk, and there may even be an uncontrolled leakage of oil from the rectum. If many fatty acid crystals are present the stool tends to have a metallic lustre, compared by Pratt to aluminium. Variations in the melting-point of the excreted fat have been noted. Von Ehrmann found that in icteric patients the melting-point is lower. One would imagine that the composition of the fats in the diet would contribute chiefly to this variation, unless certain fats are split more readily than others and the fats of lower melting-point least easily absorbed in absence of bile.

Salomon states that an obvious excretion of fat in the stools is an unequivocal sign of pancreatic insufficiency, and Tileston regards macroscopic steatorrhea as conclusive evidence of pancreatic disease, excluding of course the well-recognized excessive fat excretion due to jaundice, which has special characteristics. He considers that *complete* pancreatic achylia can be diagnosed just as readily by simple naked-eye and microscopic methods as by the use of absorption experiments and complicated tests. But the difficulty is more likely to arise in cases of a less downright character. Nor is there altogether reason for complete satisfaction with the evidence given by the fat content of the stools; for example, in a case of congenital family steatorrhea fully reported in this Journal last year by Garrod and Hurtle a persistent and obvious steatorrhea was present, but no other trace of evidence to incriminate the pancreas. The converse is equally true as seen by Keuthe's case of complete atrophy of the pancreas—a full analysis of the faecal fat gave normal figures in every respect. In another reported by T. J. Walker the patient had steatorrhea for nearly thirty years, but showed no other sign of ill health. Post-mortem examination revealed a pancreas almost entirely replaced by fat and having calculi within the dilated duct. Hence any dogmatism in interpreting an examination of fat excretion, whether with positive or negative indications, is not yet justifiable.

Fat may be present in the faeces in three chemical forms—neutral fat (glycerin esters of fatty acids), free fatty acids, and soaps (mineral salts of fatty acids). The function of lipase, a normal constituent of the external secretion of the pancreas, is to hydrolyse neutral fat into glycerin and free fatty acid. The latter, in presence of the alkali normal to the intestinal contents, combines to form soaps.

It is usually considered that the only source of origin of lipase is the pancreas, and if this be so the proportion of neutral fat in the faeces would appear to be an index of lipolytic action, and to that extent an index of pancreatic sufficiency. From researches made by Boldyreff and Brugsch it appears possible, however, that lipase may be secreted in the succus entericus from the intestinal mucous membrane. Either this or the presence of accessory nodes of pancreatic tissue may explain such cases as that of Keuthe, to which reference has already been made. Again, in some forms of pancreatic

disease, notably acute pancreatitis, the urine may contain lipase (Opie, King), and this fact suggests the presence of lipase in the blood and a possible excretion by way of the intestinal mucous membrane.

In general, modern experience bears out Müller's earlier finding of a high percentage of unsplit fat in cases of pancreatic disease, values of about 40 per cent. being common instead of the normal finding of 20 or 30 per cent. Fitz in a very valuable series of cases emphasized this point, nine out of his eleven cases having an increased ratio of neutral fat. Coming to recent work, however, one finds that in nine analyses of the faecal fats of pancreatic patients given by Pratt in 1912, only five gave neutral fat percentages of more than 30, although in other respects some of the analyses indicated abnormal fat digestion.

Whatever be the true explanation there seems no doubt that the degree of lipolysis is not always an index of pancreatic function, since in cases of very complete pancreatic disease there may be perfectly normal fat splitting, e.g. one may quote cases of:

	<i>Fat splitting.</i>
Pratt. Carcinoma of pancreas . . . . .	96
Keuthe. Atrophy of pancreas . . . . .	94
Von Ehrmann and Krüspe. Chronic pancreatitis . . . . .	88
Oskar Gross. Atrophy and fibrosis of pancreas . . . . .	92

On the other hand, in Pratt's case there was a patent duct of Santorini, so that if sufficient lipase was still formed in the diseased gland, it had a way of exit, while in von Ehrmann and Krüspe's case there may well have been some functioning part remaining in the gland. On the whole, therefore, it seems probable that a deficient lipolysis gives very strong evidence in favour of extensive disease of the pancreas, but a finding of normal fat splitting seems to prove nothing with respect to the pancreas.

Zoja, as long ago as 1899, regarded a low percentage of soaps as pointing to pancreatic disease, and von Ehrmann has noted the same fact. From a consideration of many detailed analyses it appears that a more important indication is the ratio of soaps to free fatty acids. This in normal cases is more than unity, but in pancreatic cases the ratio very frequently becomes inverted. Tileston considers that an excess of soaps over fatty free acids renders pancreatic achylia improbable, nor does he regard the absence of bile together with pancreatic juice as causing alterations in fat splitting and saponification. Bile, however, undoubtedly increases fat absorption, whether by aiding saponification and emulsification, or by some more specific action; and so in considering the analysis of faeces very careful allowance has to be made for the presence or absence of bile in the intestine.

Closely associated with fat splitting is the process of fat absorption. The proportions of free fatty acid and of soaps would appear to be dependent upon the efficiency of fat-absorption processes, and the proportion of soaps is affected

by the reaction of the intestinal contents, by their rate of passage to the rectum, and possibly by the activity of bacterial enzymes. Von Ehrmann in a case of chronic pancreatitis reported in 1910 found lowered fat splitting (57 per cent.), and in the split fat a high proportion of free fatty acid compared with soaps, 3:1, a phenomenon thought to be favoured by pancreatic insufficiency. Delfino, reporting a case of pancreatic cyst, gave very similar proportions. Now to illustrate the difficulty of drawing conclusions, in 1913 von Ehrmann reported another case of chronic pancreatitis, very closely resembling his first case, but with a totally different fat analysis—split fat 88 per cent., and ratio of free fatty acid to soaps 3:5.

Figures such as these have led several authors to suggest that absorption of fat, as apart from lipolysis, is another and separate function of the pancreas. Falta and Oskar Gross have advanced the view that an internal secretion of the pancreas controls fat absorption—internal because extracts of pancreas such as Pankreon given by the mouth do not always improve absorption. In the experience of Gross there was even a worse absorption after giving Pankreon, and Pratt with the same preparation found very little benefit. Von Ehrmann (1910) with pancreatin found very definite improvement, and Mosenthal reported favourably of administration of raw pancreas of the sheep. Gross, however, in his very elaborate research got no improvement on using pig's pancreas, so that one cannot ascribe the poor effect of Pankreon to deterioration of the product. Besides, Tauber in a special investigation on the effects of administration of Pankreon found an increase both in fat splitting and fat absorption, and he considered that in absence of icterus, the demonstration of improved fat assimilation by the use of Pankreon speaks for pancreatic achylia, or at any rate hyposecretion.

Gross's theory of an internal secretion of the pancreas subserving fat absorption finds some support in the work of Jansen, who tested the effect of removing the pancreatic external secretion from the intestine of dogs, retaining at the same time any internal secretion by means of transplantation of a portion of the gland. In such circumstances about 80 per cent. of the fat intake was absorbed. On removal of the transplanted portion a gradual increase in fat excretion set in, leading eventually to exportation of the animal's own tissue fat, as well as of exogenous fat. These experiments certainly point to a very intimate association of the pancreas with fat assimilation, but it is worth remembering that under the conditions of Jansen's experiments the whole metabolic mechanism, not only for fats, but for proteins and carbohydrates, was of necessity profoundly affected, whilst the final complete removal of pancreatic influence would assuredly react upon the whole scheme of ductless gland control.

There certainly is a tendency at the present day to oppose every fresh difficulty with an additional internal secretion. In this instance so many other factors may well be concerned to bring about a diminution of fat absorption that one hopes to dispense with the services of this particular hormone.

In connexion with Gross's theory it is interesting to note several cases of exophthalmic goitre in which fatty stools were observed. Bittorf reported one case of his own and referred to six of Falta's. In Bittorf's case there was also creatorrhoea and absence of trypsin in the stools, whilst administration of Pankreon caused a remarkable improvement in fat utilization; it seems possible that in this instance the pancreas primarily was at fault, leading through default to hyperthyroidism. Cohn and Peiser have described five cases of pancreatic disease with characteristic signs also of hyperthyroidism. The hyperthyroidism was thought to follow a hypertrophy of adrenal action as a consequence of pancreatic atrophy.

The influence of diet both on fat splitting and absorption has attracted attention. Garrod and Hurtley in their case of steatorrhoea found the total fat excretion on any diet averaged fairly constantly about 25 per cent. of the intake. With a smaller intake, however, the proportion of fat split was much higher; it must be remembered that in this patient there was no other evidence whatever of any pancreatic lesion. In one of Gross's cases of chronic pancreatitis the effect of a diet consisting mainly of milk and butter was compared with other known diets. The fat absorption showed practically no changes and about 45 per cent. of the intake was in every case utilized, but the degree of lipolysis was greatly enhanced; no explanation of these observations was advanced by their author. Von Ehrmann and Krüspe have suggested that lipase regurgitated into the stomach may act, prematurely as it were, to split the fat in the diet, thus accelerating absorptive processes in the small intestine.

This question of the site of lipolytic activity certainly deserves attention. Oser many years ago pointed out that there was often lipase in the stomach present either as a product of regurgitation or from a gastric origin, and workers in Pawlow's school have shown the influence of fats in the stomach to set up regurgitation from the duodenum, and have applied the same in a practical method of investigation—the oil-test breakfast. Fat splitting presumably takes place normally high up in the small intestine, and relative differences in the absorbability of free fatty acids and their several soaps will cause the composition of the faecal fat to be more or less unrepresentative of the true state of affairs in the small intestine. Further, the sooner and the higher up in the alimentary tract that lipolysis occurs, the greater is the opportunity for absorption of the products of lipolysis. This may help to explain some of the recorded results of fat analyses which at present require a fuller interpretation. Von Ehrmann also pointed out the influence of bacterial enzyme action in the large bowel tending to increase the fat splitting as measured by analysis of the faeces. An automatic regulation of such activity was suggested, the excessive free fatty acid production tending to inhibit bacterial growth and so to limit further formation of adventitious enzymes. Upon a combination of such influences the authors prefer to base their explanation of facts observed, rather than invoke the aid of an hypothesis of an additional internal secretion directing fat absorption.

Absorption is undoubtedly complicated by many circumstances. The con-

dition of the intestinal mucous membrane may itself preclude absorption if there is tuberculous ulceration of the bowel or amyloid disease. Secondly, rate of peristalsis is an important factor, sufficiency of lipase being more or less nullified if the intestinal contents pass very quickly. The reaction of the digesting mass will affect not only lipolysis but also saponification. Pekelharing has suggested that the enzyme remains attached to the fatty acid molecule that it has set free, until released by the union of alkali with acid. If so, lack of alkali will influence directly lipolysis and saponification.

To sum up:

1. In cases of pancreatic disease the total fat (per cent. of dried faeces) and the percentage of split fat *may* be normal.
2. Where no pancreatic disease is demonstrable the total fat may be excessive. If this is so, a normal degree of fat splitting is usual, although acute diarrhoea may prevent adequate lipolysis. The reaction of such faeces is usually alkaline and the soaps exceed the free fatty acids.
3. If the fat excretion relative to the intake exceeds 20 per cent., and if administration of pancreatic preparation improves utilization, then there is strong probability of pancreatic disease.
4. In general, if the total fat be much over 30 per cent. of the dried faeces one suspects—
  - (1) Pancreatic insufficiency ;
  - (2) Biliary insufficiency ;
  - (3) Intestinal anomalies of absorption or peristalsis.

The last two are usually characterized by a high percentage of split fat, and this in the case of biliary obstruction is usually in the form of soaps. If the percentage of split fat be low, say less than 60 per cent., there is strong presumptive evidence of pancreatic disease. When the total fat excretion is normal or subnormal the degree of fat splitting does not appear to have any significance for diagnosis. Finally the problem, as met by the clinician, is frequently complicated by the simultaneous disease of the pancreas, with stomach, liver, bile-ducts, or intestines ; in fact it is difficult to find a case where all the other conditions, e. g. gastric juice, bile secretion and exit, intestinal absorption, are completely normal, and so in every case other functions in addition to fat digestion ought to be investigated.

#### *Estimation of Lipase.*

Lipase in the faeces has been estimated by the method of Staniek, but seeing that the method is complicated and that many authorities regard the intestinal mucous membrane as a source of lipase, and in addition also the gastric mucosa, the value of such estimations is debatable. The corresponding estimations of diastase and trypsin offer practical advantages over lipase. Von Ehrmann's method for gauging the lipolytic activity of the duodenal contents is



well spoken of by Wertheimer; it depends upon the regurgitation of pancreatic juice into the stomach on giving a meal of Palmin. By lipolysis the fatty acid is set free and is subsequently extracted by a petroleum-ether-benzol mixture, and by subsequent treatment of the extract with a copper acetate solution of known strength. Thus a colorimetric and quantitative method of estimating lipase is achieved.

The method is obviously complicated and open to many objections in theory and practice, nor can one imagine every patient being able to retain 75 grm. of Palmin. The most serious objection, however, is the variation in regurgitation through the pylorus: unless this is uniform the method has no claim to be quantitative, and no advantage over many other qualitative tests.

#### *Diastatic Power of Faeces.*

Opinions vary very greatly about the utility of estimating the diastatic power of the faeces. Hirayama, Oppenheimer, and Werzberg all contend that as diastase is formed not only in the pancreas but also in the intestine such estimations have no value. Wynhausen, Wohlgemuth, Balint and Molnar, Hirschberg, and Albu have all spoken in favour of this test, and Albu especially, while recognizing objections in theory, nevertheless on practical grounds regarded it as one of the simplest and best single methods for recognizing an insufficiency of pancreatic secretion.

Liftschütz recently has shown that although the succus entericus and the bacteria of the intestine both form a diastatic ferment, this is of much less intensity than the pancreatic diastase, and so the error introduced thereby into an estimation of faecal diastatic power is not so great as to render the method of no avail in practice.

Hawk worked out an amended edition of Wohlgemuth's method and incidentally showed that copious water drinking increased permanently the amylolytic activity of the faeces, improving carbohydrate absorption, and probably also fat utilization—a suggestive idea for therapeutic application. Hawk's results were all expressed in terms of dry faeces, and this principle Rotky considers the only sound one for quantitative purposes. He regards the influence of salts present as very important and recommends that the salt content should be standardized. Nevertheless the variations in diastatic power of faeces are wide even in normal persons, and the limits have yet to be fixed; but Rotky thinks a value much below 100 units is a strong indication of pancreatic disturbance.

#### *Lecithin in Faeces.*

In 1898 Deucher first pointed out that in pancreatic diseases lecithin is often present in the stools in much increased proportion. In a normal person the total in a day's excretion is about half a gramme, equivalent to 0.1 gramme of



phosphoric acid. Apparently lecithin normally is nearly all split by the action of pancreatic juice and by that only (Glaessner), so that with deficiency of this juice more lecithin comes through unchanged. In pancreatic disease the total lecithin has been shown to reach nearly 4 grammes (= 0.8 gramme phosphoric acid).

The method involves making an ethereal extract of the twenty-four hours' faeces and estimating from this the phosphoric acid, so that it cannot be classed among the simpler clinical tests. Von Ehrmann's experience points to a diminution of lecithin splitting where pancreatic juice is deficient, and an enhanced excretion in consequence; but he points also to the influence of bile on absorption of lecithin products, and it seems quite likely that lack of bile may be a more important factor in producing a high degree of lecithin excretion than lack of pancreatic juice. The influence of the latter was demonstrated in Caro and Wörner's case of pancreatitis with fat necrosis, by a raised lecithin excretion.

There are, however, not many records of work done on this subject. Peritz, in an investigation of the relationship of parasymphilitic conditions to lecithin, made many analyses of lecithin in serum and in faeces, and showed that in the diseases mentioned the lecithin content of the serum is enhanced, as also the excretion of lecithin in the faeces. A study of Wallis and Schölberg's paper dealing with the properties of lecithin as found in pseudo-chylous ascites shows what a high degree of complexity characterizes the behaviour of lecithin within the body, so that in certain of its compounds it is not soluble in ether, and it is clear that the quantity of lecithin found in the faeces is dependent on many factors. The value, however, of this indication for clinical purposes has not been disproved, and the claim of Glaessner seems reasonable, that if after giving lecithin in increased quantity only a normal amount be found in the stools, this finding excludes pancreatic insufficiency.

#### *Glycosuria and Diseases of the Pancreas.*

To discuss adequately the relationship of glycosuria to pancreatic disease would require a consideration of so many points of fact and of theory as to lead one greatly astray from the real goal of this review, a study of the diagnosis of pancreatic disease. It will be sufficient for present purposes to discuss how far the presence or absence of glycosuria can be utilized as a guide in diagnosis.

The intimacy of the relationship between the pancreas and the control of carbohydrate metabolism is not disputed at the present day, but the exact part played by the gland is uncertain, just as the particular cells taking part in this function are not certainly determined. It is not easy to prove that the onset of glycosuria when of true pancreatic origin is an index of the severity of the disease of the gland, although a search through the literature of the subject shows that glycosuria is usually present in the more serious forms of pancreatic disease, such as cyst, calculus, or acute inflammatory or haemorrhagic conditions of the gland; we find that in chronic pancreatitis there may often be no trace of

glucose in the urine. This also happens in some cases of carcinoma, so that it appears that in just those forms of pancreatic disease in which it is possible for some of the cells still to perform their functions is glycosuria more often absent. Nevertheless, the existence of any parallelism between the degree of glycosuria and of pancreatic disease is not established, nor does there seem much evidence to prove the specific control claimed for the islet cells.

Cambridge (*Practitioner*, May, 1914) gives from his own experience the following figures in connexion with pancreatic disease and glycosuria:

Cases of glycosuria with evidence of pancreatic disease . . .	30 %
Cases of pancreatic disease accompanied by glycosuria . . .	7.4 %

In other words, in his experience the presence of glycosuria alone means a 1:3 chance that the pancreas is diseased, but in cases of pancreatic disease only one in fourteen has glycosuria. Viewed arithmetically, therefore, glycosuria is not a sign of great diagnostic value; as a practical matter, however, if together with glycosuria there is other evidence of pancreatic trouble, then glycosuria has a strong confirmatory value.

In this connexion must be mentioned alimentary glycosuria as an early sign of disability of carbohydrate metabolism. The subject is briefly discussed in my paper (*loc. cit.*) to the effect that in presence of other features pointing to lack of pancreatic efficiency, the existence of alimentary glycosuria affords strong confirmatory evidence. But its absence has little or no value for excluding pancreatic disease. Even in cases of acute pancreatitis there may be no frank glycosuria, at any rate for a time, as King reported in one of his cases; but in this instance there is little doubt that a test of glucose tolerance would have revealed alimentary glycosuria, since in the later stages glucose appeared in the urine. In a well-known case of atrophy of the pancreas, published by Keuthe, where there was evidence of impaired tryptic digestion, tests of glucose and carbohydrate toleration revealed a very slight glycosuria *ex amylo* and more definitely *e saccharo*. At autopsy a very small atrophied pancreas was found, but a small proportion of parenchyma and of 'islet' tissue was present, evidently sufficient to control an ordinary intake of carbohydrate.

The presence of portions of accessory pancreatic tissue is not unknown (Serra), and it is evident from post-mortem experience and animal experiment that quite a small node of such tissue might suffice to keep the carbohydrate balance steady. Garrod in his Lettsomian Lectures enumerated several disorders in which there has been found lowered glucose tolerance, namely, febrile conditions, pregnancy, alcoholism, certain nervous diseases, exophthalmic goitre and acromegaly, in addition to affections of the pancreas. It is a fair question to ask if, in the febrile conditions named, there may have been an associated mild inflammatory process involving the pancreas, but to do more than suggest this is in the present state of our knowledge quite unjustifiable, although the occurrence of pancreatitis in mumps is fairly often found, and Goldie recently reported cases of scarlet fever and diphtheria which were followed by pancreatitis and

jaundice. With regard to pregnancy, exophthalmic goitre, and acromegaly, in all there is good reason to believe that the inter-relationships of the hormones of the body are in a disturbed condition, and it seems quite possible that it is through the pancreatic factor in this chemical system that the carbohydrate balance suffers displacement.

Leaving hypothesis and conjecture, in practice the tolerance of the patient for glucose should be tested whenever the soundness of the pancreas is in question. In conjunction with other signs a lowered glucose tolerance lays the gland under grave suspicion, although on the other hand absence of alimentary glycosuria affords no proof of a healthy pancreas.

#### *The Cammidge Test and its Developments.*

Very much attention has been paid to the reaction devised by Cammidge in 1904 and known by his name. The test itself has undergone many vicissitudes, but despite the favourable experiences of a few workers, one must admit that the high expectations first formed have not been fulfilled. It is only fair to insist that the author of the test himself has always spoken in guarded terms of the reliability of the reaction as a pathognomonic of pancreatic disease unless taken in conjunction with other factors.

In the experience of very many German workers such as Glaessner, Mayesima, Hess, Roth, Langer, and others, and of Americans at the Mayo Clinic, and J. B. Deaver; of Libertini, and Lovatt Evans, and from my own trials, the test for purposes of diagnosis does not appear to be of practical assistance. Others such as Maass, Caro and Wörner, Kehr, Schmidt, Albu, Hagen, and Pilcher have been favourably impressed, so that a wholesale condemnation of the test will not find it without supporters. It is notable that a good many negative reactions have been recorded in cases of acute pancreatitis, e.g. by Körte (in six cases), Eichler and Schirokauer, Kehr, and Sladden. Whatever its value in diagnosis the test remains an interesting phenomenon worthy of further research, and Cammidge himself is the first to recognize this fact. Recently he has made further advances into the subject which appear to fulfil a description given by Albu, who termed the reaction 'a highly interesting pathological curiosity which will in all probability supply us with a contribution towards the solution of intermediate carbohydrate metabolism'.

Briefly Cammidge's latest conclusions are that the test is an index, not necessarily of pancreatic disease, but of a disturbance of carbohydrate metabolism which may or may not be associated with disease of the pancreas. This conclusion puts the whole matter on a broader basis, although it throws over any claim to specificity in the test, and it can only be regarded as a step forward on which its author is to be congratulated. Obviously more experience of Cammidge's 'Iodine Coefficient' method is required before his view can be

unreservedly accepted, but in a review of the subject an outline of his new test is desirable. The hydrolysis of certain urines, followed by elimination of glycuronic acid and subsequent treatment with phenylhydrazine, leads to formation of osazone crystals with definite characteristics, the crystals of the 'pancreatic reaction'. Some authors—Neuberg, for instance—maintain that there is not complete elimination of glycuronic acid, and that the osazone crystals are a glycuronic acid compound. But although it has never been proved that these crystals are those of a pentosazone it has always seemed probable that this is the case.

In his latest method Cammidge subjects the hydrolysed urine to steam distillation and finds in the product furfuralhyde presumably formed from pentose derivatives in the urine. This he estimates quantitatively by Jolles's method. He arrives in this way at an index of the amount of pentose formed in the urine; in normal healthy urines the index is zero, but in certain cases of disturbed carbohydrate metabolism it may rise to as much as 200 in a twenty-four hours' excretion of urine. It is significant that addition of various hexoses does not lead to a raised index, but that 0.1 grm. of a pentose raises it to about 30.

Cammidge's view is that in certain disturbances of carbohydrate metabolism a small quantity of a dextrin-like substance is excreted in the urine, and that from this substance on hydrolysis, a pentose is split off. This pentose is the source of the osazone crystals of the 'pancreatic reaction', and of the furfurol which gives the 'iodine coefficient' of his new method. It is significant that the urines of 'pancreatic cases' in which it is claimed that this abnormal 'dextrin-like' substance is present contain also, as proved by many observers, an abnormally high percentage of diastase: it is an interesting question whether the two phenomena are both dependent upon an aberrant carbohydrate metabolism, or whether the increased diastase content of the urine (or of the blood) may not be a cause of the presence of dextrin in the urine. Cammidge finds that when there is definite glycosuria the iodine coefficient may become lowered, and he inclines to regard the figure as an index of slight impairment of carbohydrate metabolism leading to excretion of partially hydrolysed starch in the form of dextrin into the urine. If this impairment increases, and glucose utilization becomes definitely lowered, then with the establishment of persistent glycosuria the amount of intermediate product (dextrin) passing into the urine diminishes. The reason for this diminution is by no means clear unless one assumes that the organism, after a persistent attempt to break down its carbohydrate in orderly sequence from the starches through the dextrins and glycogen to glucose and at the same time to utilize all the glucose, is forced to abandon the struggle, and allows the glucose to overflow, as it were, so that the failure becomes a failure to utilize all the glucose formed, rather than a leakage of intermediate products into the urine. If the argument can be upheld by observed facts it promises to be a powerful weapon for diagnosis, prognosis, and treatment of cases of glycosuria and of pancreatic disease. The method of

procedure is complicated and only to be performed by a trained pathological chemist, nor is it possible for the ordinary clinician or clinical laboratory.

Where there is both a leakage of dextrin bodies and failure to utilize glucose, Cammidge regards the prognosis as bad, the indication being a serious and unamenable break-down of carbohydrate metabolism.

In this connexion the experiences of Langer with the older Cammidge reaction are of considerable interest. He found the reaction not specific for pancreatic disease, but that if the subject were given 100 gm. of dextrose, insufficient to produce glycosuria, but presumably throwing considerable strain on the process of utilization of glucose, a positive 'pancreatic reaction' was induced in the urine.

Obviously these newer observations will require much detailed work before they can be accepted for purposes of generalization. Of the 'pancreatic reaction' as an aid to diagnosis the balance of opinion appears to be adverse, but its scientific interest remains and may lead to further knowledge.

#### *Excess of Diastase in the Urine.*

The presence of diastase in normal urine has been recognized for many years, for Cohnheim in 1863 demonstrated the power of urine to digest starch; but the application of previous observations towards the diagnosis of pancreatic disease is of recent date, and is due principally to Wohlgemuth in the first instance. Since 1908, when his first contribution to the subject was made, a considerable output of work on the subject has been forthcoming, but by far the most informative paper of recent date is that of Dudley Corbett.

After devising a simple method of estimating the diastatic power of urine, Wohlgemuth found that in cases of pancreatic disease the amount of diastase in the urine was remarkably increased, perhaps due, as Schmidt suggests, to obstruction in the duct causing diastase to pass into the blood in larger amount. There certainly appears to be some increase of diastase in the blood serum as a consequence of traumatic pancreatic lesions according to Noguchi's evidence. Wynhausen, Hirschberg, and Albu all obtained results confirming Wohlgemuth's observations, and later Corbett, in a research dealing with the subject on a broader basis, obtained equally significant results. Lovatt Evans, from the biochemical point of view, criticized Wohlgemuth's method, but Corbett's experience seems to uphold the method as suitable, at any rate for clinical diagnostic purposes, and it is noteworthy that Evans himself finds that the results are most reliable where there is relatively little enzyme present. This is the condition in urines of all kinds, even the most strongly diastatic urine having less than one thousandth part of the diastatic power of normal saliva.

Corbett's work shows that the blood normally contains a little diastase, and that the normal kidneys excrete about the same quantity in the urine. An increase in the diastatic power of the urine may therefore be due either to



increase of diastase in the blood, or to increased permeability of the kidney. In renal disease, there is as a rule a diminution in the urinary diastase, except in some cases of marked albuminuria, in which apparently there is increased permeability. Corbett suggests that this is due to 'automatic' passage of the relatively small colloid molecules of diastase through the damaged kidney, rather than to an increased excretory activity in that organ. Geyelin, in an extensive study of the same subject, came to a similar conclusion and found the majority of normal readings in cases of chronic nephritis to be obtained from urines containing considerable albumin. He suggested either an acceleration of the enzymic action by albumin, or an augmentation of excretion. This effect of albumin has to be reckoned with in nephritic cases.

The influence of concentration, and of salts in solution in the urine, has attracted attention: such influence is considerable, but not apparently overwhelming in most cases. Löb found an acceleration from inorganic phosphates, and the work of Cole and of Hawk shows the influence of cations and hydroxyl ions to depress activity. Diet appears to have but little effect; pyrexia, if acute, was found by Corbett to be accompanied by a raised diastatic figure, but the highest values of all were in cases with pancreatic lesions and in toxæmias of pregnancy. So marked were these last values that he suggested the possibility of involvement of the pancreas in the latter condition.

It is of interest to note that Wohlgemuth and Noguchi found increased diastatic value of the blood and the urine in cases of injury to the pancreas both in men and in animals. Delfino, in a case of pancreatic cyst, also obtained a high index, while von Ehrmann (1913) in an instructive comparison of tests in two cases of chronic pancreatitis with jaundice, and of chronic jaundice, obtained a high reading in the first patient, and a normal one in the second.

By the kindness of the author, I have been enabled to see in advance a paper contributed by Mackenzie Wallis to the July number of the *St. Bartholomew's Hospital Reports*; here his readers will find further corroboration of the value of this test in the diagnosis of pancreatic disease, together with many practical points on the method and technique of the test.

There appears to be no doubt that a high diastatic value of the urine offers considerable presumptive evidence in favour of pancreatic disease, whilst a low or normal value, provided there is no renal disease, indicates a healthy pancreas. Several writers have suggested that the test is successful only in acute stages of pancreatic disease. Analysis of the cases recorded does not bear out this view, for a positive outcome of the test appears to have been reached in every kind of pancreatic lesion. The test is relatively simple, rapid, and also clean, a point not of supreme importance but welcome none the less; further, if the patient is acutely ill the method is still applicable provided that the necessary urine can be collected. Finally, the clinical application of the test can be made very extensive, seeing that by the use of toluol as a preservative the urine may be kept without deterioration and dispatched to the clinical pathologist for examination.

The Wohlgemuth method of estimating diastase may equally well be applied



to the examination of duodenal contents obtained by intubation or by the oil-test breakfast. In either case, however, the risk of contamination with saliva is great, so that a negative finding only would be reliable.

*The Adrenalin Mydriasis Test of Loewi.*

It has been found that in certain circumstances adrenalin solution will produce dilatation of the human pupil, and upon this phenomenon is based Loewi's test. A very full *résumé* of the whole subject was compiled by Cords in 1911, and I have found reference to this monograph of great assistance.

Essentially the appearance of adrenalin mydriasis in normal man and in certain animals is dependent upon the dosage, which varies for different species. In normal man a thorough instillation of the conjunctival sac with  $\frac{1}{1000}$  solution of adrenalin does not lead to an appreciable mydriasis. If, however, a small quantity of the same solution be injected into the subconjunctival tissue mydriasis ensues within five minutes, and it is maximal within twenty minutes. In other words, if sufficient adrenalin reaches the iris, the dilating effect is produced; this point is emphasized in practice by the observation that in presence of an injury to the corneal surface in a subject otherwise normal, adrenalin readily causes mydriasis.

The exact mechanism of the action of adrenalin upon the iris is not completely understood, but the presence of a receptor substance in the muscle seems probable. Differences in the amount of this receptor would account for the varying degrees of adrenalin mydriasis obtained in different animals.

Cords gives two main conditions in which adrenalin mydriasis occurs:

1. Where there is increased activity of both the sympathetic system and the dilator pupillae muscle.
2. Where there is disturbed equilibrium of the internal secretions of the body in the direction of a preponderance of the chromaffin system.

Under the first heading he includes the condition of localized 'adrenalinæmia' ensuing upon a subconjunctival injection of adrenalin, and causing increased sensitiveness of the pupil to the action of adrenalin, but the condition would appear to resemble rather that of a disturbed equilibrium of the internal secretory system. If the influence of the superior cervical sympathetic ganglion upon the iris be removed by section or otherwise, adrenalin mydriasis ensues within two days, after a preliminary miosis. If, however, section is made below the ganglion (preganglionic section) no adrenalin mydriasis follows, thus showing that the ganglion itself exerts some special influence upon the pupil.

Adrenalin mydriasis has been observed in man in the following conditions:

1. Functional diseases of the pancreas.  
     Hyperthyroidism.  
     Diabetes mellitus.  
     Graves's disease.

## 2. Lesions of peritoneum.

" " stomach.

" " intestine.

## 3. Some diseases of the central nervous system and meninges.

A satisfactory rational explanation of this mydriasis is not yet forthcoming, although the author of the test and others have advanced ingenious speculations to account for the phenomenon.

Loewi's original work was the outcome of researches on diabetes, approaching the subject from the standpoint of the theory of excessive sugar mobilization. His argument was that sugar mobilization is directly guided by stimuli passing to the liver by the sympathetic system. These stimuli, however, in turn are subject to control of a chemical nature, which he ascribed to a depressor substance originating within the pancreas. When the pancreas was diseased this internal secretion, with its depressor influence, would be diminished, and the sympathetic system would show increased excitability. As a convenient and readily tested criterion of the degree of irritability of the sympathetic, Loewi selected the reaction of the pupil to adrenalin solution. He was unable, however, to trace an exact parallelism between the presence of adrenalin mydriasis and the presence of glycosuria, but his work clearly proved the existence of a very definite relationship between the pancreas and adrenalin mydriasis, and it is rather surprising that comparatively little attention has since been paid to the subject.

It seems that the failure to show any constant association between diabetes and adrenalin mydriasis has resulted in discrediting the whole phenomenon with most observers. But although the original theoretical basis of the test is probably far from correct, further investigation of the underlying facts is certainly called for. Pemberton and Sweet in a summary of previous work done upon the influence of the adrenals over the pancreas conclude that intravenous injections of adrenalin (and of pituitary extract) will inhibit the normal flow of pancreatic external secretion initiated by secretin, or by the arrival of gastric chyme in the duodenum. This effect persists after the systemic blood-pressure has become normal, but Pemberton and Sweet traced a correlation between blood-pressure and pancreatic flow suggesting that both features may be controlled by the percentage of adrenalin in the blood. No quantitative proof of this suggestion was achieved, however. Nor is investigation of the subject at all simple, for any operative interference with the pancreas for purposes of observing its external secretion must of necessity lead to an abnormal state of every phase of the activity of the gland. In my own experience the test has given interesting and encouraging results, though whether it will prove ultimately to be a reliable guide for the diagnosis of pancreatic disease is yet uncertain.

In view of modern ideas on the correlation of accelerator and depressor influences arising in the various glands of internal secretion, it would be rash to lay too much stress upon the pancreas alone in connexion with adrenalin mydriasis. Nor is the antagonism between pancreas and adrenals as yet clearly

established to be a fact. Reference to the remarks on the subject by Gley and others at the International Congress of last year shows how many objections can be raised against this theory of antagonism. But in my view it is equally rash to dismiss the phenomena observed as empirical and absurd.

It is significant that in hyperthyroid conditions adrenalin mydriasis is often present, perhaps as an expression of the increased activity of the chromaffin system as opposed to the depressor group of glands. For cases of exophthalmos Cords, however, suggested the simpler explanation of corneal inflammation leading to rapid absorption of adrenalin—excessive dosage in fact.

Zak, whose experience of adrenalin mydriasis as a functional test of the pancreas was not favourable, obtained positive results in many cases of abdominal disease, in peritoneal, gastric, and intestinal lesions. If it can be shown that the test is very sensitive to changes in the pancreas, then a positive outcome of the test might occur frequently with a secondary inflammation of the gland, arriving perhaps by the lymphatic route (Deaver); but if such is the case its value for diagnosis diminishes greatly.

One point seems clear: it is not a satisfactory test for diabetes mellitus, and the fact that Loewi originally investigated it from that standpoint has apparently obscured the undoubted importance of the phenomenon from the more general aspect of pancreatic function. Another point in its favour is the large proportion of negative tests in very varied conditions, as shown in my paper referred to. Finally, when compared with any other test tried for investigating pancreatic functioning, Loewi's test surpasses all in the ready and simple manner of its performance, an additional reason to practical clinicians for giving it a fair and unbiased trial.

#### *Conclusion.*

To summarize the present position of diagnosis of pancreatic disease is not a simple matter. For those who expect one absolute and pathognomonic sign to be found the outlook is not encouraging, for it does not seem likely that any one test of pancreatic disease, and that alone, will ever be discovered. The functions of the pancreas are so manifold that only in completely destructive pathological conditions are they all in abeyance. Further, when this is the case some of the functions, especially those subserving digestion, may be more or less effectively performed by other means within the body, and this fact more perhaps than any other depreciates very considerably the value of many tests based upon the efficiency of pancreatic ferments. A partial disablement of the gland may, however, cause a diminution in the power of one or more of the ferments in the external secretion, but no reliance can be placed in a quantitative estimation of such ferment action as an index of the degree of pancreatic disease.

Still more is this so in the case of tests based upon more obscure functions

of the pancreas dependent upon its chemical relationships with the rest of the body, for a very small amount of healthy gland tissue can serve to maintain the chemical balance and disguise any process of disease. It is evident also that a complete occlusion of the duct of Wirsung will produce profoundly different changes according as the accessory duct of Santorini is patent or not. Duct occlusion, too, may or may not affect the production of internal secretions, at any rate in the earlier stages of such conditions. Nor can the possibility of absorption of ferments be dismissed, and it may well be that our present classification of external and internal secretions of the pancreas may have to be modified, since enzymes of the digestive secretion, e.g. diastase and lipase, can both be demonstrated in the blood serum, and all the evidence points to a pancreatic origin for these ferments in the blood.

The varying influences of disease processes upon the different parts of the gland have yet to receive a much clearer explanation. The usual classification of pancreatitis is based upon the origin of the inflammatory process; from the blood-vessels, from the ducts and gland acini (ascending infection), or from adjacent viscera, as in cases of duodenal ulceration. Deaver and Pfeiffer, however, have laid stress upon the lymphatic route as an important and frequent mode of infection, and, in the case they described, giving rise to an interlobular pancreatitis. One would expect in an ascending infection a more immediate effect upon the externally secreting cells of the gland; also in an interlobular pancreatitis one would expect the gland acini to have their activity less impaired than in the interacinar variety.

So far, however, little success has attended attempts to correlate the mode and severity of infection of the pancreas with the clinical signs and symptoms; the data are yet insufficient, and the more immediate problem is not a differential diagnosis of pancreatic lesions so much as the answer to the question, Is the pancreas healthy or diseased? This answer is best got by calling in the aid of as many witnesses as possible, always remembering that the evidence of any one test may be neglected if at variance with the evidence of the majority, and that in summing up, sight is never lost of the clinical aspect of the case.

To come to practice, our first question when the pancreas lies under suspicion must be, What kinds of tests can we apply in this instance—simple tests only, or more elaborate methods requiring a well-equipped laboratory and expert assistance? In either instance as many tests as possible should be made, and if the more elaborate methods are not available, then microscopic examination of the stools for creatorrhoea and steatorrhoea, and tests for glycosuria, actual or alimentary, should be applied. The adrenalin mydriasis test I should certainly try in every case, although with a healthy scepticism, and finally in most cases it should not be difficult to get the diastase of the urine estimated.

In the case where a laboratory is at call, that is to say for patients at either end of the social scale, a more extensive investigation can be tried in addition

to the tests already mentioned, and here certainly the urinary diastase should be estimated, and a complete analysis of the faecal fat be made. Metabolism experiments on fat and nitrogen utilization, with and without pancreatic extract, are very desirable, and either the oil-test meal or duodenal intubation may with advantage be tried in suitable cases, together with examinations of the diastatic and tryptic power of the faeces by the casein method. For the better establishment of their use rather than for their present value in diagnosis one would like to see extensively tried the iodine coefficient of Cammidge, and the lecithin content of the stools.

Of course, to use all these methods as a routine is a counsel of perfection not likely to be attained in many cases, but I have indicated what appear to be the most promising lines of investigation towards the solution of a problem full of difficulties both in theory and in practice.

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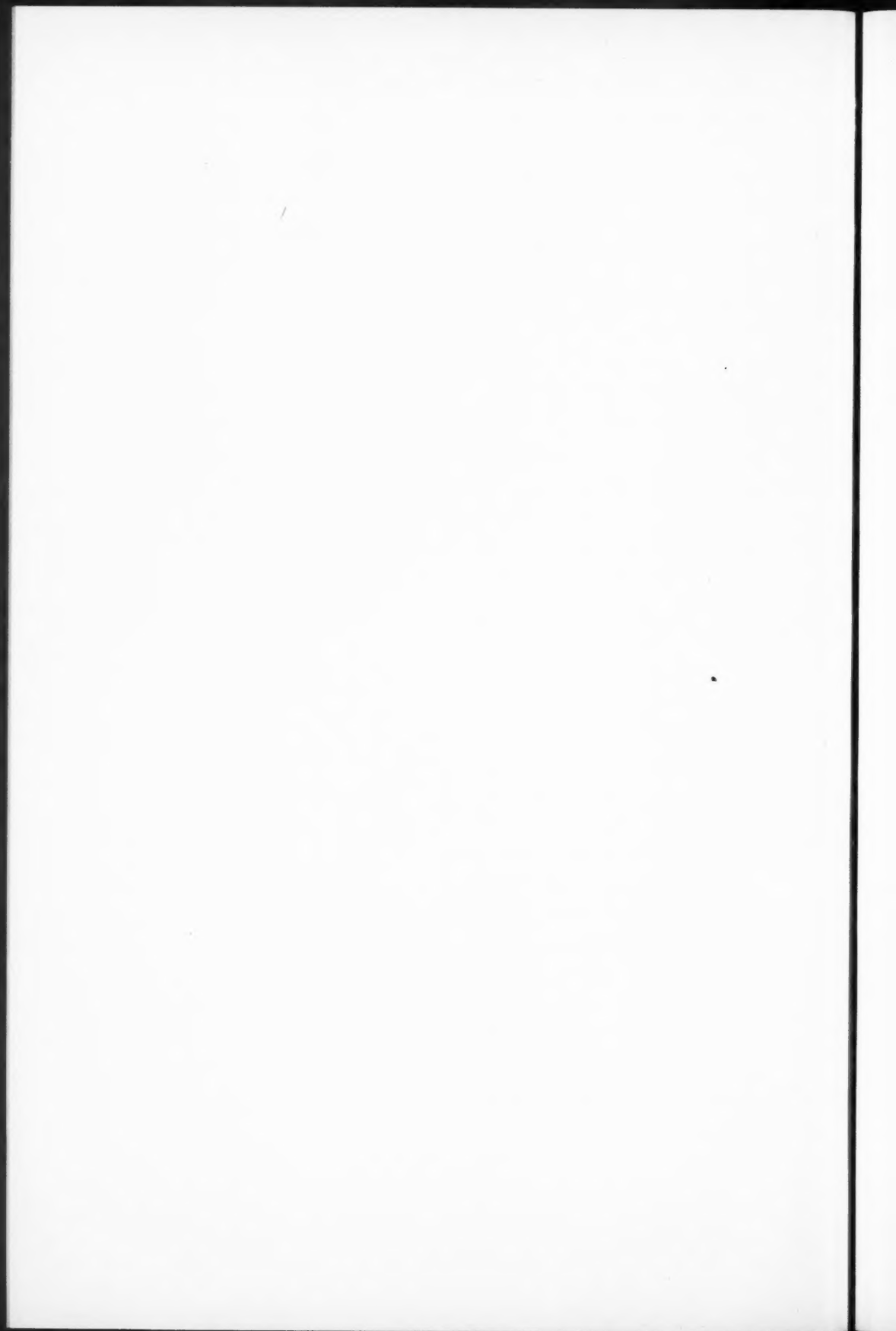
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PROCEEDINGS OF THE ASSOCIATION OF PHYSICIANS  
OF GREAT BRITAIN AND IRELAND

EIGHTH ANNUAL GENERAL MEETING

THE EIGHTH ANNUAL GENERAL MEETING was held at Cambridge on Friday and Saturday, March 20 and 21, 1914.

The Sessions were held in the Lecture Theatre of the Examination Hall, by kind permission of the University Authorities.

The President, Dr. G. S. Middleton, was prevented by illness from being present. The Regius Professor, Sir Clifford Allbutt, K.C.B., was accordingly voted into the chair.

The Minutes of the previous Meeting (1913) were read and confirmed.

The President, Officers, and Committee were elected as follows for the ensuing year:

*President:* Professor Sir T. CLIFFORD ALLBUTT, K.C.B.

*Treasurer:* Dr. HALE WHITE.

*Secretary:* Dr. HERRINGHAM.

*Members for England:*

Professor A. G. BARRS.  
Dr. D. DRUMMOND.  
Dr. LAURENCE HUMPHRY.  
Professor G. MURRAY.  
Dr. WILLIAM PASTEUR.  
Dr. F. J. POYNTON.

*Members for Scotland:*

Dr. BYROM BRAMWELL.  
Professor ASHLEY MACKINTOSH.  
Dr. BARCLAY NESS.

*Members for Ireland:*

Professor JAMES CRAIG.  
Dr. McKISACK.  
Dr. GEORGE PEACOCKE.

The following were elected Members of the Association :

BARNES, A. E., M.B., 34 Wilkinson Street, Sheffield.

BOXWELL, William, M.D., 2 Upper Hatch Street, Dublin.

CHISOLM, R. A., M.D., 37 Queen Anne Street, W.

DIXON, W. E., M.D., F.R.S., Pharmacological Laboratory, Cambridge.

FINDLAY, Leonard, M.D., 7 Newton Terrace, Glasgow.

GOW, A. E., M.D., 46 Ridgmount Gardens, W.C.

GRAHAM, George, M.D., 12 Ladbroke Gardens, Notting Hill, W.

[Q. J. M., July, 1914.]

KENNEDY, A. M., M.D., Kenmill, Bothwell.

LEA, C. E., M.D., 124 High Street, Oxford Road, Manchester.

MACILWAINE, J. E., M.D., 26 College Gardens, Belfast.

MALDEN, Walter, M.D., 58 Lensfield Road, Cambridge.

PARSONS, Leonard G., M.D., 52 Newhall Street, Birmingham.

RYFFEL, J. H., M.B., Guy's Hospital, S.E.

VEALE, R. A., M.D., 37 Park Square, Leeds.

WALL, Cecil, M.D., 10 Cavendish Place, W.

The Treasurer then presented his accounts, showing a balance to the credit of the Association. He asked for leave to employ some of this, not only, as usual, in the payment of writers of critical reviews, but also in the occasional provision of illustrations in the *Quarterly Journal of Medicine*. The Meeting signified its assent.

The President then called upon Dr. Judson Bury, who invited the Association to meet next year at Manchester. The President, having put the question to the Meeting, declared the invitation to be accepted with cordial thanks.

### SCIENTIFIC BUSINESS

Dr. HUGH THURSFIELD described a case of acholuric jaundice cured by splenectomy, and referred to others. He mentioned the importance of the fragility of red blood-cells as a symptom of congenital cases. In acquired cases the same operation had often been performed with success. The operation had also been performed successfully in cases of pernicious anaemia. In these, estimation of the fat in the blood, and of urobilin in the stools, had been found of importance. These operations were too recent for a judgement as to their results. In the Gaucher type of splenomegaly the indications were against operation, and in von Jacksch disease (pseudo-leukaemia infantum) the prognosis was so good that operation was not advisable. In the early stages of splenic anaemia operation seemed, if not to cure, at least greatly to improve.

Dr. J. R. BRADSHAW related the history of a case of splenic anaemia in a boy of 17 on whom the operation was performed, and showed the spleen and the patient. The latter appeared to be in very good health.

Dr. GALLOWAY referred to a case in which the operation had not been followed by improvement.

Dr. ROLLESTON stated that splenectomy might benefit (a) by removing the mechanical cause of haemorrhage, or (b) by removing a source of poison. He thought Dr. Gibson's cases in which a streptothrix was discovered were so various in nature that the parasite could hardly be of prime importance. He laid stress on the serious nature of the operation.

Dr. POYNTON thought it difficult to decide when splenectomy should be performed for congenital acholuric jaundice. Some such cases improved greatly; some as they reached adult life became subject to severe attacks of pain; in some the blood deteriorated. In the two latter classes operation might be of use.

Dr. PARKES WEBER, from experience of a family which was subject to this disease, would hesitate to recommend splenectomy. These patients lived long, and in good health. For pernicious anaemia the operation was too recent for the evidence to be reliable. In splenic anaemia the operation was dangerous in the later stages, and uncalled for in the earlier, since the prognosis was often favourable.

Dr. GIBSON had found the streptothrix in Dr. Bradshaw's case. He was now attempting to cultivate the parasite, and had in one case succeeded.

Dr. CHARLES and Dr. HALE WHITE related cases.

Sir WILLIAM OSLER said that (1) many cases of splenomegaly did not suffer with any ill health, (2) some had mechanical difficulties due to the size and mobility of the

spleen. Such spleens might be fixed without removal. (3) Recurrent haemorrhage was the most serious danger, but often depended upon oesophageal varices which were not removed by splenectomy. (4) Recurrent anaemia and (5) early jaundice and ascites were definite indications for operation.

Dr. WILLIAM HUNTER was not able to accept the current classification or terminology.

Dr. HARRY CAMPBELL spoke on the intrathecal treatment of tabes dorsalis and general paralysis, mentioning three cases in which Mr. Ballance had injected the salvarsanized serum into the lateral ventricle.

Dr. JOHN NIXON spoke on the use of salvarsan in concentrated solution. He injected 2 to 4 mg. of neosalvarsan in less than 10 cc. of water, by means of an ordinary syringe, directly into the external jugular vein. This method had no disadvantages and was much less painful.

The Members then separated to see the following demonstrations in the Physiological Laboratory:

1. Drs. T. S. HELE, GOWLAND HOPKINS, C. S. L. WOLF, and Messrs. S. W. COLE, R. A. PETERS, and ff. ROBERTS.—The Determination of Blood Constituents, &c., upon Minute Quantities of Blood Material.

- (a) Total non-protein nitrogen;
- (b) Amino-acid nitrogen;
- (c) Urea and ammonia;
- (d) Uric acid;
- (e) Sugar;
- (f) Chlorides;
- (g) The hydrogen ion concentration.

2. Mr. J. BARCROFT.—The Blood Gases: the Dissociation Curve of Haemoglobin in Health and Disease.

3. Miss D. DALE and Mr. G. R. MINES.—Demonstration with the Frog of the Effects of the Removal of Calcium on the Electro-cardiogram.

#### FRIDAY AFTERNOON, 3 P.M.

Professor JAMES LINDSAY related a case of Landry's paralysis, fatal, but without autopsy. He discussed the diagnosis, and while allowing that many cases once thought to be of this might now be referred to other types, believed that there were some, of which his own was one, which formed a class of themselves.

Dr. ERNEST REYNOLDS agreed in both opinions, and mentioned cases which, though he had at first believed them to be of this type, he had later considered to be influenzal.

Dr. FOORD CAIGER related a rapidly fatal case.

Dr. FRED BATTEN thought Dr. Caiger's case was probably one of acute poliomyelitis, and had never seen a case of Landry's palsy.

Dr. STANLEY BARNES had seen a true case in which the most minute examination had been made without the discovery of any lesion or infection. He had seen two cases since. He thought that in some cases the disease was chronic.

Dr. WARRINGTON referred to cases of rapid recovery.

Dr. JUDSON BURY emphasized the sensory symptoms as an essential part of Landry's description.

Dr. PURVES STEWART mentioned the importance of examining the cerebrospinal fluid.

Dr. FRED BATTEN spoke on familial forms of progressive cerebral degeneration in children, and related three instances in a family of five children, marked by loss of sight and loss of mind, fatal about 6 years of age, and showing during life peculiar pigmentation about the macula, and also in the periphery of the retina, and after

death degeneration of the large pyramidal cells of the cerebrum, and of the Purkinje cells of the cerebellum.

Dr. HAMILL described a study of cases with Cheyne-Stokes respiration. He had found that the pulse quickened directly after respiration began, and that the blood-pressure rose as the respiration began. He concluded that the low blood-pressure was the result of asphyxia, but was due less to the presence of  $\text{CO}_2$  than to the absence of  $\text{O}$ , for the blood-pressure could be maintained, or if low, raised, by inhaling  $\text{O}$ . In patients with a permanently high blood-pressure, dyspnoea could be produced if it were lowered. This could be removed by digitalis. Cases of nocturnal dyspnoea could be relieved by digitalis.

Dr. SUTHERLAND asked whether the action of digitalis in these cases was direct, or was produced by removal of arrhythmia.

Dr. F. J. SMITH asked for the experience of others as to the prognosis of Cheyne-Stokes respiration.

Dr. HOBHOUSE related a case.

Sir WILLIAM OSLER drew attention to the normal Cheyne-Stokes respiration of healthy aged persons, and of sleeping children.

Sir CLIFFORD ALLBUTT corroborated him.

Dr. HALE WHITE mentioned a case of the kind in which the acidity of the blood was much raised. It was anticipated that the vessels serving the medulla would be found diseased. They were, on the contrary, the healthiest in the body, but yet the respiratory centre was found to be much degenerated.

Dr. ROBERT HUTCHISON spoke of the common association of achylia gastrica and pernicious anaemia. It was commonly held that the latter caused the former. But, in addition to other evidence, he had had a case in which achylia, shown by chemical tests, preceded a fatal case of anaemia, and others in which symptoms indicating achylia, especially a dislike of meat, were related in the previous history of anaemic patients.

Dr. ARTHUR HERTZ confirmed the importance of gastric tests in the diagnosis of pernicious anaemia. These were the smallest stomachs seen with X-rays. Their contents passed with abnormal rapidity, and there was often diarrhoea.

Dr. WILLIAM HUNTER agreed. He thought that the state of the stomach might be accurately inferred from the condition of the tongue. Sore tongue was extremely common in these cases. It led to an atrophy which was the result of a neuritis. The neuritis was probably due to the same toxin as that which caused the haemolysis.

Dr. WILLIAM RUSSELL spoke on the determination of the right border of the stomach by auscultatory succussion and percussion.

Dr. HERTZ stated that the method was entirely unreliable, and that nothing could compare in value with the X-ray method.

A large number of Members then drove out to Mr. Strangeways' Research Hospital, where they were taken round the Museum by Mr. Strangeways and Mr. Marrack. The specimens of various arthritic conditions were of the greatest interest and beauty.

In the evening the Annual Dinner was held in the Hall of Christ's. The thanks of the Association were formally tendered both to the Cambridge Members for their admirable arrangements, and to the Master and Fellows for lending their beautiful Hall and rooms. Dr. Laurence Humphry and Professor Hobson responded.

#### SATURDAY MORNING, MARCH 21.

Mr. J. E. MARRACK gave the results of elaborate estimations of the metabolism of patients with rheumatoid arthritis, acute and chronic. There appeared in neither case to be any definite deviation from the normal. There was in particular no increase of acids, organic or inorganic, no unusual excretion of calcium, and no evidence of intestinal putrefaction.



Sir JAMES BARR discussed the results.

Sir WILLIAM OSLER spoke in the highest terms of the serious character of the work, and of its importance. He asked whether any one had seen a case of real recovery.

Dr. POYNTON thought that use could well be made of the experimental arthritis produced in animals by the injection of streptococci, for the lesions were very similar.

Dr. BUCKLEY was of opinion that in some cases the process during acute stages was atrophic (osteoporotic), while the deposition of fresh bone (osteophysis and osteosclerosis) was a mark of the chronic stage of the disease, or of a greater resistance on the part of the patient.

Dr. LAURENCE HUMPHRY described a case of abdominal tumour due to the kick of a horse. The chief symptom was uncontrollable vomiting. The urinary diastase index was high, and there was a trace of sugar. Loewi's reaction (dilatation of pupil by adrenalin) was positive. On this evidence the tumour was rightly diagnosed as pancreatic. The autopsy showed a large cyst. He asked for opinions on the value of pancreatic tests.

Dr. GARROD thought that we must not expect any pancreatic test to be of universal value. He had used Loewi's test widely and had found it positive in all pancreatic cases, and very rarely positive in any other. Loewi originally used it as a test of peripheral sympathetic irritability in dogs whose pancreas had been removed. The diastase test was also of value.

Mr. MACKENZIE WALLIS had found the index of urinary diastase very high in all proved cases of pancreatic disease. The estimation of fat in the faeces was another good test. Sahli's test (pot. iod. in stearin capsules) was not very useful owing to the long stay of the capsules in the stomach. The test for the preservation of the nuclei in beef cubes, in thymus tissue and lycopodium, given in silk bags, was not satisfactory. Einhorn's duodenal tube was not well reported on.

Dr. GARROD drew attention to cases of glycosuria without hyperglycaemia. Glycosuria might be produced (i) by an overdose of sugar, (ii) by interference with the glycogen function, (iii) by interference with the tissue-absorption—in each case with hyperglycaemia. But if the kidneys are abnormally permeable for glucose, there would result glycosuria without hyperglycaemia. This could be produced artificially by phloridzin, and it appeared also to occur naturally. The diagnosis depended (a) upon the direct estimation of the sugar in the blood, (b) upon the failure of a large dose of sugar to increase, and of a restricted diet to decrease the glycosuria, (c) upon the absence of ill health. But there seemed in some of these cases to be a family connexion with true diabetes. The sugar was always true glucose.

Professor SAUNDBY referred to the condition in three sisters, all healthy.

Dr. HILL ABRAM mentioned such a patient who had no ill health himself, but whose son died, aged 7, of diabetes.

Dr. SPRIGGS gave an account of a patient with pancreatic disease. The motions were very large, and their passage exhausting. They contained 40 % of solids, and of the solids 73 % were fat. Trypsin, which occurs in normal faeces, was absent here. The patient had glycosuria, which was easily removed by rest and diet. His tolerance could be then much increased. Of the fat taken, 50 to 100 % was excreted in the faeces. Over 90 % of it was split, showing that the amount split was of little importance as a test, and was probably due in this case to bacteria.

Dr. SYMES had had a similar case which lasted for many years.

Mr. MACKENZIE WALLIS questioned the value of some of the tests used.

Sir WILLIAM OSLER related seventeen cases of nephritis with purpura or urticaria, or angio-neurotic oedema, of which five had died with uraemia, three had become chronic, and the rest had cleared up, though often with long persistence of albuminuria. Dropsy was rare, albuminuria great, tube casts present.

Sir CLIFFORD ALLBUTT questioned whether such cases should be called nephritis.

Dr. ARTHUR HALL had had one of these cases. The patient died with uraemia.

The Members then attended the following demonstrations in the Pharmacological Laboratory :

1. Professor WOODHEAD.—The Morbid Anatomy of Pneumonic Plague (Manchuria); materials sent by Dr. Wu Lien Teh.
2. The Quick Professor (Professor NUTTALL).—Parasitological Specimens.
3. Dr. W. E. DIXON.—On Cerebrospinal Pressure.
4. Dr. W. M. SCOTT.—Auriculo-ventricular Inco-ordination, produced by Ethyl-hydrocuprein.

And in the Psychological Laboratory :

5. Dr. C. S. MYERS.—Psychological Apparatus.

#### SATURDAY AFTERNOON, 3 P.M.

Professor WARDROP GRIFFITH described a case of patent ductus arteriosus with infective endocarditis. The diastolic murmur disappeared towards the end of life owing to the duct being blocked by a warty growth on the wall of the pulmonary artery. These cases of patent duct were sometimes complicated with coarctation of the aorta, in which case the current set from the pulmonary to the aorta, and the right ventricle was hypertrophied. In all other cases the current set the reverse way.

Dr. JOHN FAWCETT mentioned that similar murmurs occurred when an aortic aneurysm opened into the pulmonary.

Professor WARDROP GRIFFITH then described three cases in which the heart-block was *prima facie* partial, but really complete.

Dr. TYSON discussed the cases.

Dr. CAREY COOMBS spoke on *a.-v.* conductivity in rheumatic heart disease. He had investigated and tabulated a series of cases. He showed that the incidence of failure of conductivity increased with age, that heart-block was often seen in mild cases, was usually transient, and usually incomplete, and that neither phenomenon was common.

Dr. NAISH said that of ten recorded cases of heart-block in acute rheumatism seven showed microscopic evidence of disease in the 'bundle', while three were negative. His own case showed marked myocarditis in the bundle.

Dr. DRYSDALE considered delay an earlier stage of heart-block.

Dr. SUTHERLAND asked whether a 3 to 1 heart-block with a rapid pulse was really a block, or merely the result of inability to respond to the very rapid stimulus of the auricular contraction.

Dr. ALEXANDER MORISON was less inclined than others to think conduction a necessary part of the mechanism, and more inclined to allow independent contraction of auricle and ventricle.

Dr. LEWIS SMITH asked what was the prognosis.

Professor WARDROP GRIFFITH replied that heart-block undoubtedly occurred without organic lesion, as under digitalis, or in asphyxia. True, the ventricle usually took commands from the auricle, but probably in unusual conditions it took charge independently. Some cases of heart-block lived for many years.

Dr. HAWTHORNE instanced the *pulsus alternans* to show that sphygmometric were not true readings of blood pressure. The strong beats needed 175 mm. and the weak only 130 mm. Hg for obliteration. *Pulsus alternans* was sometimes only brought out when the armlet was applied. Was there more inequality in the force of the cardiac beat than was usually allowed? A patient of his own who was still alive had *pulsus alternans* five years ago.

Dr. HUME stated that out of forty cases of diphtheria eighteen had showed some failure of conduction. The first group was severe and fatal, and occurred early in the disease. There was in this group no characteristic change in the *a.-v.* node, but much fatty change in the ventricular muscle. The second group showed a severe onset, with rapid pulse and serious heart weakness. The symptoms appeared late, forty or fifty days after the onset of diphtheria. In this group there was neither nodal nor myocardial degeneration. But in both groups there were patches of interstitial carditis. The third group was mild, and showed only occasional extra-systoles.

Dr. D. B. LEES said that it was important to examine the heart carefully in every case of diphtheria.

After a few words of farewell from the President the Meeting then broke up.